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REGULATION OF HUMAN TISSUE TRANSPLANTATION

HEARING

OF THE

COMMITTEE ON LABOR AND HUMAN RESOURCES UNITED STATES SENATE

ONE HUNDRED SECOND CONGRESS

SECOND SESSION

ON

S. 2908

TO AMEND THE PUBLIC HEALTH SERVICE ACT TO PROVIDE REASONABLE ASSURANCES THAT HUMAN TISSUE INTENDED FOR TRANSPLANTATION IS SAFE AND EFFECTIVE, AND FOR OTHER PURPOSES

SEPTEMBER 29, 1992

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REGULATION OF HUMAN TISSUE TRANSPLANTATION

TUESDAY, SEPTEMBER 29, 1992

U.S. SENATE,
COMMITTEE ON LABOR AND HUMAN RESOURCES,
Washington, DC.

The committee met, pursuant to notice, at 9:20 a.m., in room SD–192, Dirksen Senate Office Building, Senator Paul Simon presiding.

Present: Senators Simon and Dodd.

OPENING STATEMENT OF SENATOR SIMON

Senator SIMON. Good morning. The hearing will come to order.

We are holding this hearing on the difficult area of human tissue transplant. Every year, more than 10,000 tissue donors supply more than 500,000 pieces of tissue for transplantation in the United States. There is no uniform method to assure appropriate donor screening for tissue and to track the tissue, once it is donated. There are no national standards for the tissue themselves and no oversight of tissue banks.

Tissue transplantation does not need regulatory overkill, such as the kind FDA exercised in June of 1991 by announcing that replacement human heart valves would be regulated as Class III medical devices. I might say that is how I got involved in this. The University of Chicago came to me and told me FDAs decision creates a very severe problem for them.

I think there are some general principles that we ought to bear in mind, and I have introduced legislation that is based on them. But our views are not set in concrete. We are not going to pass anything this session.

I think it is clear that we need to do something and I hope that Congress, working with the FDA and HHS and others, can come up with something that is sound.

Those general principles seem to me to be the following: First, both the tissue bank community and the Federal Government have the responsibility to the public to assure the safety of human tissue.

Second, human tissue should not be regulated as if it is an artificial product designed by human beings. And third, the regulation of human tissue should be by a single regulatory mechanism developed either through statute or by an agreement among the FDA and the tissue transplantation community.

The medical community believes that appropriate regulation of heart valve allografts will have positive results. Dr. Richard A. Jonas, Associate Professor of Surgery at Harvard Medical School, points out, however, that "even the slightest interference with the availability of the human valve at this crucial time would result in a definite increase in operative mortality for complex conditions."

According to information provided to the Circulatory Systems Advisory Panel, there are approximately 1,400 to 1,500 valves presently processed, and this is an inadequate number to meet current demand, so that any delay or reduction in numbers has a severe impact.

[The prepared statement of Senator Simon follows:]

PREPARED STATEMENT OF SENATOR SIMON

Every year more 10,000 tissue donors supply more than 500,000 pieces of tissue for transplantation in the United States. This tissue includes bone, heart valves, veins, tendons, ligaments, cartilage, nerves, arteries, dura mater and connective tissue. Every year, scientific and medical advances—and increased demand for tissues—increase the role of tissue transplantation in medical practice.

Certainly the lives of many have been made better by tissue transplantation. Some people owe their lives to it. Yet there are risks. There is the risk that the discomfort and expense of transplantation will not yield the intended result. Even worse, there is the risk that transplanted tissue may bring harm, that it may transmit new, perhaps even fatal, diseases. This risk was tragically demonstrated when three persons became HIV-positive recently as a result of transplantation of tissues from a Virginia donor.

I share the concern of many that there is no uniform method to assure appropriate donor screening for tissue and to track the tissue once it is donated. There are no national standards for the tissues themselves and no oversight of tissue banks.

But while tissue transplantation needs regulation, it does not need regulatory overkill such as the kind FDA exercised in June of 1991 by announcing that replacement human heart valves would be regulated as Class III medical devices. Treating a wholly human product as if it were a manufactured device requiring investigational device exemption and premarket approval application is not just illogical; it also jeopardizes the availability of human heart valves—which are often the only type of heart valve transplant that will work for infants, children and pregnant women—and it threatens reimbursement for the cost of surgical procedures and the tissue itself by public programs and private medical insurance.

These are some of the reasons why I introduced S. 2908, the Human Tissue Transplantation Act of 1992. Under S. 2908 the Secretary of Health and Human Services would establish a National Council on Tissue Transplantation. The Council would develop voluntary professional standards for tissue and tissue banks.

The Secretary of HHS then would promulgate those standards or more stringent ones if necessary to ensure the safety and efficacy of transplantation tissue. The Secretary would also license tissue banks that meet the standards.

Finally, S. 2908 would rescind the current time-consuming and unwieldy FDA regulation of human heart valves under the medical device statute and replace it with expedited public standards for types of human tissue.

Today we will hear from the FDA, the National Tissue Bank Council, the American Association of Tissue Banks, the American Red Cross, CryoLife Cardiovascular Inc., and the Director of Pediatric Cardiac Surgery of Georgetown University. I look forward to the testimony of our witnesses and to finding a workable and safe alternative to the patchwork and piecemeal regulation of human tissue for transplantation.

Senator SIMON. We are here to learn from our witnesses and we are very pleased to have as our first witness Michael Taylor, the Deputy Commissioner for Policy at the Food and Drug Administration.

I might add that Commissioner David Kessler called me yesterday and expressed an interest in this. He is, like me, open to ideas, and we look forward to learning in the hearing today.

I am very pleased to have you here with us, Mr. Taylor.

STATEMENT OF MICHAEL R. TAYLOR, DEPUTY COMMISSIONER FOR POLICY; ACCOMPANIED BY ANN WION, OFFICE OF GENERAL COUNSEL; GORDON JOHNSON, CENTER FOR DEVICES AND RADIOLOGICAL HEALTH; AND JAMES WEIXEL, OFFICE OF HEALTH AFFAIRS, FOOD AND DRUG ADMINISTRATION, ROCKVILLE, MD

Mr. TAYLOR. Thank you, Mr. Chairman.

We do appreciate the opportunity to be here today to discuss the regulation of human tissue and your bill, the Human Tissue Transplantation Act of 1992.

With me today, on my far right, are Ann Wion, with the department's Office of General Counsel; on my immediate right, Dr. Gordon Johnson, with FDA's Center for Devices and Radiological Health; and on my left, James Weixel, with FDA's Office of Health Affairs.

I do have a written statement we have submitted for the record and I will try to present——

Senator SIMON. I might mention, for all the witnesses, that we will enter your full written statements in the record, if you wish to make oral presentations.

Mr. TAYLOR. Thank you, Mr. Chairman.

As you know, we at FDA and in the Public Health Service are currently evaluating how best to ensure that the public health issues posed by the growing therapeutic use of transplanted human tissue are properly addressed. We are engaged in discussions with various tissue banking entities, professional organizations and other interested parties, to learn more about the issues and how they might best be addressed. We are going to share with you today some of what we have learned, focusing, though, on the questions we believe must be addressed in devising any new regulatory scheme for tissues.

Let me reemphasize at the outset, though, as Dr. Kessler has already done, that we do appreciate your initiative in introducing this legislation. Dr. Kessler and all of us at FDA know this is a

critically important area that deserves all of our thoughtful consideration, and we look forward to working with you and other members of the committee to be sure that our Federal regulatory efforts serve the public health in the most efficient and productive way.

As you know, FDA has been involved in the regulation of human tissue products for some time. Our Center for Biologics Research and Evaluation has been regulating blood for decades under the authorities of the Public Health Service Act and the Federal Food, Drug and Cosmetic Act. Other tissue derived products, such as human hormones, have also been regulated as drugs and as biologics.

Transplanted human tissue may also be subject to regulation by FDA under the 1976 Medical Device Amendments, and again, as you are well aware, several categories of human tissue are being regulated as medical devices. These include corneal lenticules, dura mater allografts and, of course, heart valve allografts.

While FDA regulation of human tissue is not new, developments in recent years have prompted the Public Health Service and FDA to take a fresh look at our regulatory tools and practices. One important development has been the rapid technological progress in the field of tissue transplantation, which has greatly expanded the actual and potential uses for human tissue for important therapeutic purposes. This progress is positive and exciting, because of the benefits it has delivered and promises to deliver to patients. I want to assure you that FDA recognizes and values those benefits and takes them into account, as we do our regulatory work.

As the use of tissue has expanded, however, we have become increasingly aware of public health issues that need to be addressed. One of these developments, of course, is the possibility of HIV and other infectious disease transmission. Another is the increasing use of innovative processing techniques for tissues, but also increasing questions about whether the processing techniques affect the safety or utility of the tissue.

Our current review of tissue regulation is intended to determine the proper role for Federal oversight in assuring that these questions of tissue safety and utility are adequately addressed.

The discovery in 1991, of course, that seven people had been infected with the HIV virus through transplantation of organs and tissues from a seronegative donor sparked discussion within the tissue bank community and PHS of how the risk of infectious disease transmission could be reduced. A PHS task force was convened and, after consideration of the issue, including 2 days of public hearings, the task forced recommended to the Assistant Secretary for Health, Dr. Mason, that FDA establish at least a mandatory regulatory floor consisting of registration of tissue banks, donor screening criteria and recordkeeping to track tissues.

We believe that safety related measures recommended by the PHS work group would be an appropriate part of any new Federal regulatory scheme for tissues, but we agree with the task force that they need to be considered, this floor of safety regulation needs to be considered, in the context of the broader set of safety, effectiveness and resource issues that the work group also identifies for Dr. Mason.

And there are, as you have indicated in your own opening statement, Mr. Chairman, there are additional issues that arise from the fact that the technology of tissue transplantation has developed dramatically over the last decade. As a result of these developments, many human tissues, such as bone grafts, tendon grafts, corneas, nerves and skin grafts have become an integral part of medical procedures. As tissue transplantation practices have grown, so has the number of individuals and institutions that collect, process and provide these materials, and so has the need to address questions of safety, product quality and the maintenance of the tissues' utility.

When fresh human tissue is recovered and used immediately in a patient in need, without any processing, there are a few questions about potential harm from processing fluids or about whether tissue viability and effectiveness have been maintained. But modern tissue banking has become much more sophisticated than that. Refinements in technology have permitted treatment of tissues with various chemicals and antibiotics and nutrient solutions to maintain functionality of the tissue for a longer period of time.

Cryopreservation technology permits tissue storage at very low temperatures nearly indefinitely. Packaging containers designed to permit aseptic deep-freeze storage have been developed. Tissue transplants are shipped in special containers. These preservation, storage and transportation technologies have permitted storage and national distribution of tissues previously managed locally and in a short time frame.

Each of these interventions, though, raises questions as to whether the initial safety and utility of the tissue have been preserved—questions similar to ones FDA has traditionally addressed regarding medical devices, unapproved drugs or biologics, or other medical products.

The heart valve allograft case provides an example of this phenomenon. As medical practice and technology evolved, human heart valve tissue was subjected to a variety of new processing techniques, but there was little consistency or common understanding of the best processes.

For instance, after heart valves are recovered, they are immediately placed in a solution which contains various chemicals, including nutrients and up to five different antibiotics. Over time, some heart valve processors had modified the mix of antibiotics, after finding that certain ones were too cytotoxic and resulted in damage to the valves. However, not all processing centers adapted to such new information as it was developed. Further, not all processing centers were uniformly requiring state-of-the-art donor screening and testing for their allograft tissue materials.

As you know, FDA has used its authority under the Medical Device Amendments of 1976 to address the safety and product quality issues posed by heart valve allografts. FDA has called for more standardized approaches to heart valve processing and for the generation of data validating optimal approaches to assuring the safety and quality of the tissue.

FDA has taken these actions under the provisions of the 1976 Amendments that authorized the agency to require pre-market approval—a form of individual product license—for higher health risk

medical devices, so-called Class III devices that were in use before 1976.

Now, we at FDA know from long experience in both the pharmaceutical and medical device areas that imposition of such regulatory controls on products that have well established therapeutic rolls can be disruptive and inevitably imposes costs. In the case of heart valve allografts, we have taken steps to achieve the goals of standardizing and validating the new processing technologies while maintaining continued access to this critical life saving tissue.

We have extended the effective date for the requirement that valves be covered by investigational device exemptions to allow time for the many medical centers involved to make the necessary arrangements. We have worked with HCFA to assure continued Medicare reimbursement for allograft valves, in the interest of maintaining availability and public access to them, based on their clinical benefits to identifiable subpopulations.

While FDA intervention on heart valves has certainly imposed some costs, we believe it has also conferred significant benefits for patients in the form of improved and more widely observed procedures for donor screening and tissue processing and handling. We are committed to working with the tissue bank and medical community to assure that access to heart valve allografts is maintained as we enhance the scientific underpinnings for their continued use.

Let me turn now to some future issues for consideration. As I have indicated, these developments I have discussed in the field of tissue transplantation and our experience with heart valve allografts do raise important questions about the proper role for and the best approach to Federal regulatory oversight.

The challenge is particularly acute in devising a sound approach to the retrospective application of standards to tissues and practices that already are established in clinical practice, especially when one considers the diversity of transplanted tissue products and the vast number of such materials that are in current use.

The ideal goal, of course, is to maximize the safety and effectiveness of transplanted tissue materials, in light of improving technology and increasing patient benefits, while preserving the benefits already achieved and not significantly disrupting the continued market availability of needed products.

We are actively considering this issue and, as I have indicated to your staff, will be reporting on various options to Assistant Secretary Mason in November. I would like to identify some of the questions that we think have to be answered.

We have really organized our thinking around three broad questions: First, is there a need for a comprehensive Federal program instead of the case-by-case application of FDA's medical device or biologics authority? If there is a need, should it be addressed under current law or through new legislation tailored to tissues? And finally, what are the appropriate elements for a regulatory scheme for tissues?

First, the need, the public health rationale, for Federal intervention beyond what FDA is doing now: Certainly, reducing the risk of infectious disease transmission is one possible justification for a broader Federal role, but we are examining the full array of public health issues that may need attention. We think today's hearing

will be an important start toward building the case for some comprehensive approach to Federal regulation of tissues.

If we do conclude that there is a legitimate need for a more comprehensive approach to tissue regulation, the next broad question is whether it should be pursued through new legislation or under FDA's current statutory authorities. FDA does have authority today, we believe, under the Public Health Service Act and the Food and Drug Act, to mount just about any regulatory intervention one might reasonably consider appropriate. This is especially true since the 1990 enactment of the Safe Medical Devices Act, which enhanced FDA's flexibility in managing the introduction of products into the marketplace and expanded the agency's post-marketing surveillance and data-gathering authorities.

The existing legislation was not written, however, with the full range of transplantable tissues specifically in mind, and some have suggested that even with some of their emerging similarities, tissues are sufficiently different from conventional medical products, that their regulation should be based on specially tailored legislation. Although we are still examining this question, many of us are inclined to agree that legislation is needed.

The last broad question to be addressed concerns the appropriate elements of a regulatory program. The regulatory tools available to FDA to regulate the broad range of therapeutic products fall into five categories: They are registration of facilities and products; inspection of facilities and other enforcement mechanisms; setting technical standards governing such product safety and quality related matters as manufacturing, processing, storage and distributing the products; regulatory standards and procedures to assure effectiveness and oversight of the investigational process and market entry for new products.

Any new scheme, however, needs to be flexible. Some or all of these tools may be appropriate, but to be credible, we think any new scheme must at least satisfactorily address the issues of safety; standards to assure product quality and utility; how new processes and tissue uses, including propriety ones, are to be handled; how to build on the role of private standard-setting and oversight bodies; and, finally, enforcement.

Your bill, Mr. Chairman, addresses many of these questions, but not all of them. Importantly, the bill recognizes the knowledge and experience that resides in the private sector. We also are exploring creative ways to harness that expertise.

Your bill recognizes the role that standards may be able to play as at least a partial surrogate for individual product licensing. We are very interested in exploring this approach.

As you know, many of the innovative uses of tissue transplant materials have come from independent research in the academic and medical community. Whatever scheme is developed must preserve and foster such innovation, while also assuring through some mechanism that new medical technology satisfies some agreed upon criteria of safety and effectiveness. This is an issue that the bill does not as yet address.

Finally, Mr. Chairman, any new statutory scheme obviously must provide sufficient enforcement tools to preclude outliers from

avoiding the regulatory scheme entirely, and we would have some comments on your bill in this respect.

In conclusion, as these comments I hope have made clear, while S. 2908 does not address all of the issues, we do sincerely welcome it as an expression of your interest, initiative and willingness to explore new solutions.

I personally thank you, Mr. Chairman, for the opportunity to present FDA's views, and we all look forward to working with you to develop answers to questions before us and to develop an approach that will assure that patients continue to benefit from the advances we have seen in the area of tissue transplantation.

My colleagues and I, of course, would be happy to answer your questions.

[The prepared statement of Mr. Taylor may be found in additional material.]

Senator SIMON. I thank you very much for a very constructive statement.

First, because we will be getting, both through these witnesses and others, into the question of health risk, I would just like to underscore for the record and for anyone who may be watching this on C–SPAN, your statement, "Based on the voluntary measures currently in place, we believe the risk of HIV transmission associated with human tissue transplantation is very low." You are not suggesting, nor is anyone suggesting, those risks are nonexistent, but it is not something that people have to have massive fears about.

I do this to Judy and Bob on my staff regularly here: "Cryopreservation" is what?

Mr. TAYLOR. That is preserving through freezing?

Senator SIMON. Pardon?

Mr. TAYLOR. That is a method of preserving tissue by freezing it.

Senator SIMON. I gradually learn what we are talking about in this field.

Mr. TAYLOR. If your questions get any more technical than that, Mr. Chairman, I may have to call on my colleagues to answer.

Senator SIMON. I was pleased with your statement, "We are committed to working with the tissue bank and medical community to assure that access to heart valve allografts is maintained as we enhance the scientific underpinnings for their continued use."

How long is the average interval now between application for approval of a medical device, generally, under a pre-market application and actual approval of that device?

Mr. TAYLOR. I will defer to Dr. Johnson to give you the answer, although I think you will have to understand that every medical device is different and there will be no way to generalize, I think, based on past experience.

Senator SIMON. And a follow-up question, obviously, has to do with the human heart valve allograft. Does that differ? Then the obvious question of whether the human heart valve allograft should be classified as a Class II or Class III device. We will just toss all of those either at you, Mr. Taylor, or one of your colleagues.

Mr. TAYLOR. Mr. Chairman, let me address the question of Class III versus Class II and some sense of what we see happening in the near term with respect to the submission of marketing applica-

tions, and then Dr. Johnson can talk about how they would be managed.

Senator SIMON. Maybe for the record, you could differentiate. What does Class II mean; what does Class III mean?

Mr. TAYLOR. One of the, frankly, appealing features of the 1976 Device Amendments is that it recognized that not all medical devices are the same in terms of the risks they pose to patients and the kind of controls that are needed to protect patients from those risks and assure effectiveness.

So it divided the universe of devices into three categories, Class I, Class II and Class III, with Class I being the lower risk devices, the ones that need very minimal controls and the sort of typical, perhaps overly mundane example is a crutch as an example of a Class I device. There are more sophisticated Class I devices than that, of course.

Class II devices are the intermediate category, where it is felt that formal individual product licensing is not necessary to assure safety and effectiveness, but some performance standard setting forth the basis on which the device can be safely and effectively used is necessary to protect patients. These are devices that typically pose more significant risk than Class I.

Class III devices are the higher risk devices, including most implantable devices, devices that often are life-supporting or life-sustaining devices, and these are the devices that, under the statute, are contemplated to require formal pre-market approval by FDA in order to be on the market.

The basic principle governing market access for truly new devices is that they are automatically Class III, unless there is a basis for reclassifying them to a lower classification. So that is the basic scheme, Mr. Chairman.

It is clear, based on the nature of the issues presented, including the fact that these are implanted life-sustaining devices, that the appropriate classification from FDA's advantage point is Class III.

One of the requirements for Class I is that we have information available to assure safety and effectiveness, based on performance standards or other special controls, and one of the key features of the situation with heart valves, as I think my testimony suggested, was the need to generate some additional data so that would be able to validate appropriate processing and handling techniques, and that is the central attribute of using the Class III regulatory approach for a situation like heart valve allografts. That permits us to generate and place on the manufacturers the burden of generating the data needed to validate processing and other issues relating to safety and effectiveness.

We now, of course, are in the process under the IDE's that are going to be going into effect in the near term of generating these data and providing the basis for companies to submit pre-market approval applications to the Center for Devices.

I will let Dr. Johnson talk about how they will be handled.

Dr. JOHNSON. Mr. Chairman, with reference to your question about timing and pre-market approval applications, as you are aware, there is a statutory time allocated of 180 days for review and approval of such applications. Regrettably, we are not regularly meeting that standard these days.

But with reference to heart valves specifically, the allografts, we do not yet have any applications in place. We do have the investigational device exemptions, which allow the clinical studies to proceed to gather data. And in the case of heart valves, our expectation is that with standardized procedures that will be applied by the sponsors, in this case the tissue banks that make these available, that within a reasonable period of time, what will expect to be established is that the kind of past experience, the historical experience that is being relied upon for clinical judgments, i.e., that these are safe to use and appropriate and effective, will be validated or confirmed by those studies, so our hope would be, within a reasonable period of time, that we will receive the pre-market approval applications.

As far as predictions as to what that timing would be or how long it would take for approval, it is very difficult to make that in advance.

Senator SIMON. How long will it be before we have data available for you to draw conclusions?

Mr. TAYLOR. Again, those who are currently in the process of gathering it are in a better position than we to tell you that, and I think they will be up later. We understand, at least in some cases, they may be getting very close to having the data sufficient to submit a pre-market approval application. We certainly look forward to that just as soon as possible, because we want to go ahead and bring this process to close as expeditiously as we can.

Senator SIMON. The rationale for treating a human heart valve in the same way you would a mechanical device to do the same thing seems questionable. One obviously has an experience of working and the other does not. These are things you are looking at, as you determine where we ought to go, I guess?

Mr. TAYLOR. Yes, indeed. Please understand that our standards for passing on reviewing and passing on pre-market approval applications for Class III devices is flexible enough, so that we can certainly take into account that this was not engineered by human beings. We do not have to start from scratch in understanding that these valves have utility, and the nature of the clinical evidence that we will be looking for will obviously also take that into account.

We are looking essentially to validate that the processing standards and other controls on the handling of these materials that the tissue banks are now observing, in fact, continue to produce valves that have the utility that we have a lot of experience with over a number of years. So we have a flexible standard that permits us to take very much into account that these are human tissues about which we know a great deal when we begin.

Senator SIMON. Where are you from originally, Mr. Taylor?

Mr. TAYLOR. Virginia, Mr. Chairman.

Senator SIMON. The University of Virginia Medical School says that they want to start a new tissue bank and process heart valves. Do they have to duplicate all the studies that have been made up to this point?

Mr. TAYLOR. Well, there is a substantial amount of information in the scientific literature that provides the foundation for what all

the tissue banks are doing in this area, so there is a substantial head start that any tissue bank would have.

In order to go through the full pre-market approval process under the device law, this is a feature of it that is part of why we need to take a fresh look at how well it will work over time with tissues generally, is that that new tissue bank would have to go through its own application process.

Now, it could join with other tissue banks, nonprofit or otherwise, it could pool data, as I understand is being done under some of the nonprofits, and spread that cost and minimize the burden. But under our system, it is an individual product license in the end, and they either have to join with others and be part of someone else's license or have their own and be able to submit their own data.

Dr. JOHNSON. If I might add, Mr. Chairman, under the Safe Medical Devices Act of 1990, provision was made to open up the proprietary data in pre-market applications after there have been four submitted and approved, so that it would be possible to use that accumulated data at that point in time under the present medical device legislation.

Senator SIMON. One of the things that I learned in going through this—and I have a great deal yet to learn—is that we bring tissue from other countries. What percentage of the tissue used in the United States is brought from other countries, and do we have standards for safety here?

I chair the Foreign Relations Subcommittee on Africa, and we held a hearing about 10 days ago on the whole question of AIDS in Africa. It is a massive problem in many of the countries of Africa. Is these a safety concern, as we bring in tissue from other countries?

Mr. WEIKEL. At the present time, Mr. Chairman, we have an import alert in just one tissue, which happens to be dura mater, and we are extremely concerned about unconfirmed reports that we have heard, as you have, that quantities of musculoskeletal tissue are coming into the United States from foreign countries and perhaps are being recovered from donors about whom we know nothing, and we know nothing of the screening or the testing that might have been introduced in order to protect recipients of this tissue.

But what we need is better information about the actual occurrences, rather than just rumors. We do have confirmed evidence of individuals contacting tissue banks and asking them if they wanted to participate in schemes to import tissue from foreign countries and the tissue banks declined, and we have no way of knowing what transpired subsequent to that. But we are very much interested in learning of instances where this has actually occurred, so that we can introduce regulatory practices that will arrest that process. For now, we have an asserted jurisdiction, in general, over musculoskeletal tissue, even in our own country.

Mr. TAYLOR. Mr. Chairman, If I may just add, if we can get some information about the percentage that will be useful, we will submit it for the record, but it is clearly the case that the possibility of the importation practices growing is one factor that interested us in using our authorities in the case of heart valve allografts, and

I think generally is one reason why there is a need to seriously consider a comprehensive set of federally enforceable standards for tissue, so that we will have an existing U.S. framework that we can readily apply and hold any imported tissues to, just as we would domestic tissue. I think it is an important public health issue and we should try to understand its full dimension as best we can.

Senator SIMON. Is there any evidence at this point that tissue that is imported is less safe than that we get here in the United States.

Mr. WEIKEL. We have heard reports of anecdotal evidence of the use of bone that has been imported and there were graft failures. Whether they were attributable to the integrity of the bone that was imported or not, we do not know, nor do those we have discussed this with know for certain what the actual cause of graft failure was. But there have only been a few instances where it was alleged that the material itself may have been defective in some respects and resulted in inferior outcomes for the patients.

Senator SIMON. What is the process right now to ensure safety with respect to AIDS, or to assure the quality of, say, a heart valve or other tissue?

Mr. TAYLOR. Well, the principal approach to assuring safety with respect to the risk of infectious disease transmission is to apply donor screening criteria, so that those who would be in the position to transmit HIV or other infectious disease can be eliminated from the donor pool.

Obviously, there is also a need for recordkeeping to track tissues, so that in the event that the existence of an infection in a donor is discovered after the donation, there is still an opportunity to track and retrieve tissues that have yet to be implanted and then to identify patients who have received potentially infected tissue. So donor screening and recordkeeping to track is the basic approach on——

Senator SIMON. If I may interrupt, the donor screening becomes more difficult if someone is from Europe, Asia, Africa or Latin America?

Mr. TAYLOR. Absolutely. There is a bigger question mark you have to have in your mind about imported tissues, if only because we have a very good understanding of the way in which the tissue community in the United States predominantly is handling these issues. There has been a very responsible, serious approach since the Virginia Beach incident to deal with particularly the risk of HIV transmission, and we have a good sense that we have got adequate measures in place. Obviously, we do not have the same firsthand knowledge about what is going on around the countries.

Senator SIMON. When there is that tissue transplant, is the patient notified of any information at all about the donor or the screening process?

Mr. WEIKEL. Mr. Chairman, are you speaking of instances where infection is transmitted or just as a general practice?

Senator SIMON. Just as a general practice, if I go in and get a heart valve put in, a human heart valve, will any information be provided to me about the donor?

Mr. WEIKEL. Well, the tissue bank that recovers the tissue from the donor uses screening processes that involve both testing serum

from the donor and getting medical histories and things like this from next of kin.

They in turn, by the nature of the standards that they observe and some of the accreditation inspections that are done by the voluntary organizations are, in effect, offering assurance to the hospital or the surgeon who uses this material. Some of it is implied, some it may be more expressed. But whether or not the surgeon conveys that to the individual patient is something about which we have no knowledge. Maybe some of the speakers later today could shed some light on that.

Senator SIMON. Mr. Taylor, if right now the President of the United States were to say to you "What should we be doing in this field? how would you answer?

Mr. TAYLOR. I think what I am ready to say today, as I indicated in my testimony, is that there are some issues that clearly need to be addressed by a regulatory regime. You do need to have a base floor of safety controls to deal with infectious disease transmission.

I think it is also clear that there are sufficient questions about the impact that processing and handling can have on the utility of tissues, that we ought to have some agreed upon validated standards governing those sorts of processing techniques, standards that would be enforceable, so that everybody in the business would be required to comply with those standards. I think those are central elements of a regime that would be necessary to protect public health and maintain public confidence in these technologies.

One of the issues that is yet to be resolved in our own mind is what are the circumstances in which the individual product kind of process that we are currently applying to heart valves, individual licensing sort of approach, is still necessary to protect public health, and, in particular, when would you apply that sort of individual product supervision in the innovation process and the investigational process, as new tissue uses, new processing techniques come into play. Those are questions that we are still grappling with internally. We plan to present options to Dr. Mason in mid-November and hope we have something the administration can advance the first of next year.

Senator SIMON. Let me just add, first of all, that I am impressed by the constructive testimony you have offered here today. I think the safety factor and the adequacy of supply are the two things that clearly we have to be keeping in mind.

I am pleased to be joined by Senator Dodd here today. Senator Dodd?

Senator DODD. Mr. Chairman, I apologize for being a few minutes late. I will forego any questioning at this particular time and thank our witnesses for coming.

Senator SIMON. We thank you very, very much for your testimony.

Mr. TAYLOR. Thank you, Mr. Chairman.

Senator SIMON. The next panel includes Jeffrey Sandler, Executive Director of the Mile High Transplant Bank, of Denver, CO, testifying on behalf of the National Tissue Bank Council. He is accompanied by Dr. Steven F. Gitelis, the head of Orthopaedic Oncology at Rush Presbyterian St. Luke's Medical Center, and Tissue Medical Director at the Regional Organ Bank of Illinois, in Chicago.

Also, we will hear from Dr. Charles B. Cuono, President of the American Association of Tissue Banks; and Dr. S. Randolph May, National Head of Tissue Services of the American Red Cross.

We are very pleased to have all of you here. I note, Dr. Gitelis, I have a constituent here. Senator Dodd, Dr. Cuono is a constituent of yours.

Senator DODD. He is a good friend, as well.

Senator SIMON. We are doubly happy to have you here as a witness.

What we would like to do is to enter your full statements in the record, and if you can confine your oral statements to 5-minutes—and we will have a little light going here—that would appreciated. Unless there is some preference, I am just going to start with you, Dr. May, and just go down the table here.

STATEMENTS OF S. RANDOLPH MAY, NATIONAL HEAD OF TISSUE SERVICES, AMERICAN RED CROSS, WASHINGTON, DC; CHARLES B. CUONO, M.D., PRESIDENT, AMERICAN ASSOCIATION OF TISSUE BANKS; AND JEFFREY A. SANDLER, EXECUTIVE DIRECTOR, MILE HIGH TRANSPLANT BANK, DENVER, CO, ON BEHALF OF THE NATIONAL TISSUE BANK COUNCIL; ACCOMPANIED BY STEVEN F. GITELIS, M.D., HEAD OF ORTHOPAEDIC ONCOLOGY, RUSH PRESBYTERIAN ST. LUKE'S MEDICAL CENTER, AND TISSUE MEDICAL DIRECTOR, REGIONAL ORGAN BANK OF ILLINOIS, CHICAGO, IL

Mr. MAY. Thank you, Mr. Chairman, ladies and gentlemen.

My name is Randolph May, and I am National Head of Tissue Services of the American Red Cross. As such, I speak for the 31 American Red Cross regional tissue services in 22 States.

Last year, our system supplied approximately 45,000 pieces of tissue to individual Americans for the relief of disease, trauma and suffering. This represents an estimated 20 percent of all transplantable tissue utilized in the United States, excluding corneas.

I welcome the opportunity to testify today on the subject of human tissue transplantation. More than 10,000 tissue donors annually supply more than 500,000 pieces of tissue for transplantation into our fellow Americans suffering from disease and trauma.

The rapid growth of this effective medical treatment requires increased scrutiny to protect the American public from diseases which might be transmitted via tissue. This may be accomplished by first registration and licensing of tissue banks; second, establishment of tissue-specific donor screening procedures, and, third, the use of fail-safe procedures to link donors and recipients in order to track potentially infectious tissue.

Human tissue provided for transplantation must be safe and any required regulation of tissue must increase quality and safety. The American Red Cross feels strongly that mandatory, enforceable standards are needed to assure the safety of the people who depend upon transplantable human tissue to sustain or improve the quality of their lives.

Currently, there is very little regulation of tissue and tissue banking in this country. As a voluntarily self-regulated industry,

tissue banking has served the public well and has provided safe, quality tissue for the past two decades.

However, last year, America experienced a major scare when an organ-and-tissue donor was suspected of transmitting the AIDS virus to seven transplant recipients, three organ and four tissue. Indeed, the total public harm could have been much worse, since over 58 individuals received organs and tissues from this one donor. Fortunately, the tissue was obtained and processed according to the current standards of the American Association of Tissue Banks or AATB.

The AATB currently provides voluntary standards for tissue banks and operates an inspection and accreditation program. Compliance with standards is voluntary. However, only 45 of a possible field of 400 tissue banks in this country have been inspected and certified to be in compliance with those standards. This leaves 90 percent of U.S. tissue banks uninspected and unaccredited, even on a voluntary basis, and represents significant risk to the health of the American people.

The American Red Cross urges Congress to establish a public law that requires enforceable regulations with the aim of preventing the transmission of diseases such as AIDS and hepatitis through tissue transplantation. We agree with the American Association of Tissue Banks that a mechanism is needed to require licensing of tissue bank organizations to establish tissue-specific donor screening criteria and to provide for effective and rapid tracking of tissue between donors and recipients.

Tissue banks should be required to obtain a license to operate, after they have demonstrated compliance with all requirements. Conversely, this license would be revoked, if a tissue bank was found to be operating outside of required regulations.

Second, transmissible diseases from donated tissue should be avoided by adequate donor screening, donor sample testing and sterile processing of the tissue. Tracking is more complex. Tracking organs from donors to recipients is simpler than in the case of tissues, because organs are transplanted immediately after recovery, and only a limited number of organs must be tracked from a donor. Tissues can be banked, however, and a long time may pass between recovery and transplantation. This exacerbates the difficulty of tracking tissue during a recall or a lookback procedure.

More importantly, hundreds of pieces of tissue may be obtained from a single donor, thereby involving a larger-scale tracking procedure. These differences in scale underscore the need for different regulatory approaches for tracking of tissues and organs. State departments of health and the Centers for Disease Control currently serve this tracking function well. However, communications between organ procurement organizations and tissue banks regarding the notification of infection in tissue recipients needs to be specified in the Federal regulation.

The regulation of tissues, including licensure, uniform donor screening standards and trackability of tissues between donor and recipient can be minimized by utilizing the role of the Department of Health and Human Services. If this simple solution is chosen, then the major factors in the cost of regulation will be rulemaking,

protocol writing and research into the cost and infection rate associated with tissue.

The benefits of such regulation would be heightened perception of safety in the public mind and a promotion of the types of well regulated tissue banks that would be less susceptible to failures which cause medical misadventures.

The most immediate problem relates to the current regulation of heart valves as a Class III medical device. As a Class III medical device, an investigational device exemption must be filed and then a pre-market approval submitted, yielding an extended, costly process for both tissue banks and the FDA.

Several issues present themselves. Tissue is not an investigational device or material, but is standard equipment in human beings. For example, the medical literature on transplantable heart valves begins in the 1960's and consists of hundreds of papers detailing processing use and outcome. Allograft heart valves have been successfully used in about 2,000 patients per year.

These books I am holding up are two books which review all of the medical progress on heart valves. Certainly, allograft heart valves are not experimental devices. Placing allograft heart valves in Class III and requiring IDE's for them makes them an investigational product, thus, allowing some third-party payers to refuse to cover the expense of the implant.

In such a case, if the patient desperately needing a heart valve to save his or her life is neither covered by Medicare nor wealthy enough to pay the $40,000 to $60,000 required, then they will be denied the opportunity to obtain a heart valve and they will die. Moreover, the lack of reimbursement to the nonprofit providers of heart valves may cause them not to be able to supply this precious resource, half of which is used in children.

An adequate solution to the heart valve regulatory dilemma might be for the FDA to classify these valves as Class II medical devices. In this way, the FDA will still regulate their procurement and processing, there would be no IDE requirement, the lack of third-party reimbursement would be solved, since Class II devices are reimbursed, and the appropriate level of good manufacturing practices would be applied to the processing of the valves. This appears to be the simplest, least costly and most effective solution to the difficult situation in which we all find ourselves today.

These issues illustrate that while the FDA has been appropriately carrying out its assignment in regulating tissue according to its normal procedures, these may not be flexible enough for the needs of a diverse tissue field. Yet, in the "Tissue and Organ Transplant Assessment Report, of July 18, 1991, by the Public Health Service Workgroup", it states that "FDA should proceed with their pending regulations . . . as expeditiously as possible." If the FDA is to regulate tissue, then it would be quite beneficial for that agency to develop a rational approach to tissue regulation that could be used to solve some of the aforementioned objections.

Congress should maintain the Federal regulation of human organs, tissues and cells by the Department of Health and Human Services. This will not require major realignment of agency oversight, but there may need to be an adjustment in the current regulation of tissue by the FDA.

I would like to thank the committee for allowing American Red Cross Tissue Services to share our concerns about the future regulation of transplantable tissue. Tissue banking has produced extraordinarily safe tissue on a voluntary basis for decades. Now as the field has grown and matured, we look forward to working with you to develop regulation for the safety and effectiveness of this precious resource.

Thank you.

[The prepared statement of Mr. May may be found in additional material.]

Senator SIMON. Thank you very much, Dr. May.

Dr. Cuono.

Dr. CUONO. Thank you, Mr. Chairman, Senator Dodd and ladies and gentleman.

My name is Charles Cuono and I am President of the American Association of Tissue Banks, and I present here today the association's position on the important issues raised by the Human Tissue Transplantation Act.

Having studied these issues for several years, we recognize that any program of oversight or regulation of tissue transplantation must embody three fundamental principles, and these are: First, compulsory registration of all tissue banks; second, the establishment of uniform donor screening criteria, based upon recommendations from recognized experts in the field; and, third, the establishment of a tracking system capable of reconciling each step of transit of all tissues from donor to recipient. Such a system will include a standard reporting protocol for suspected disease transmission.

Based upon our careful analysis, we conclude that S. 2908 fails to adequately address these three fundamental principles. Furthermore, in its current form, S. 2908 relies on a voluntary system, namely, the National Council on Tissue Transplantation. In almost every way, the proposed voluntary council duplicates the existing voluntary system established in 1980 by the American Association of Tissue Banks. The AATB system of oversight, I should note, is operated at no expense to the taxpayer.

It is our view that an expert study group, a panel or a task force should be convened to address these complex issues. Areas which must be examined include:

First, a tightened definition of human tissue. For example, the term "biological transplants" could differentiate biological tissues from "mechanical implants." A human heart valve, although analogous to a mechanical heart valve in terms of its function in the recipient, is clearly very different from the manufactured device. Lack of such discriminating definition in the device regulations may have contributed to FDA's current position on regulation of heart valves as Class III devices.

Second, consideration of human tissue as a biologic and/or monitor it under the statutes of both biologics and devices within the FDA.

Third, the advisability of an exemption from the usual investigational use requirements for tissues that have been in use for long periods of time and for the banks that provide them.

Fourth, the development of specific GMP's for biologic tissues, reflecting what has already been learned and formulated as the GMP's for blood and blood components.

Fifth, examination of the standards and procedures for tissue banking already developed by the American Association of Tissue Banks.

Sixth, the development of a system to track all tissues from donor to recipient and back.

Seventh, the development of a system of uniform reporting for suspected or actual incidence of disease transmission.

Eighth, the development of standard donor screening criteria which can be applied to all donors for all human tissue acquisition.

Ninth, the examination of the adequacy of training of tissue bank personnel.

And tenth, consideration for reclassification of human heart valves to a more appropriate category.

While we are firmly committed to ensuring safety of donated human tissues, we feel that our accredited member banks that provide allograft heart valves are experiencing what we believe to be an unreasonable mandate for filing applications for IDE's.

While our association promulgates standards and solicits voluntary participation by all tissue banks, we recognize that uniform nationwide compliance with established standards can only be guaranteed through mandated oversight by an external agency.

In fact, our association is currently working with the American Association of Blood Banks and the College of American Pathologists to develop effective economic systems to track disposition of human tissue for transplantation. We feel that Federal oversight of this developing national program is essential.

With the potential for increased influx of tissues to this country from foreign countries, we have addressed the issue with a panel on our upcoming international meeting to be held in Boston in 1993, at which we will discuss donor screening and standards with our European and Pan Asian colleagues.

AATB is the not-for-profit professional organization which currently represents nearly 1,000 individual and institutional members engaged in all aspects of tissue banking. Members of AATB formulate standards that govern the acquisition, preparation, distribution and banking of tissues and cells for transplantation. Our guiding philosophy in the development and promulgation of these standards and procedures has been to assure maximum safety to the recipient of tissue transplants, whether it is a bone graft to avoid amputation, skin to protect a burned area, or human heart valve to avert a life-threatening condition.

Our commitment to safety is best exemplified by our vigorous program of inspection and accreditation of tissue banking facilities, a program which we feel has had a positive impact on the impressive record of safety in human tissue transplantation. Of the estimated more than 3 million tissue transplants completed in nearly a decade since the identification of HIV, tissue from only two donors has been documented as having transmitted the AIDS virus.

Every major tissue bank in this country has voluntary applied for AATB accreditation. Of the 400 banks recognized by the U.S. Public Health Service, nearly 100 are accredited or have applied for

accreditation by AATB. Another 100 are eye banks, which are members of our sister Eye Bank Association of America, which has its own accreditation program. And a third 100 are identifiable semen banks, which will be regulated under FDA statutes for biologics. Most of the remaining banks are predominantly small hospital facilities that retrieve and store bone from living donors.

AATB's accreditation process has benefited considerably from the informal review, continuing dialogue and spirit of helpfulness which has been established and maintained over the decade with the staffs of the FDA and the CDC.

In conclusion, the American Association of Tissue Banks appreciates the opportunity to present our assessment of the Human Tissue Transplantation Act of 1992. Our recommendations are based upon our long-standing commitment to recipient safety and our 20 years experience in development of standards. AATB stands ready to assist and cooperate with the development of Federal policy to insure the safety of bank tissue for transplantation.

[The prepared statement of Dr. Cuono may be found in additional material.]

Senator SIMON. Thank you very much, Dr. Cuono.

Mr. Sandler.

Mr. SANDLER. Mr. Chairman and members of the committee, I am Jeff Sandler, Executive Director of the Mile High Transplant Bank located in Denver, CO, and a member of the Executive Committee of the National Tissue Bank Council. I am accompanied by Dr. Steven Gitelis, whose practice includes the transportation of large tissue grafts at Rush Medical Center, and who is the Medical Director of the Regional Organ Bank of Illinois Tissue Bank.

The NTBC supports S. 2908, the Human Tissue Transplantation Act of 1992, because it believes that documented public health concerns demand the establishment of uniform national standards for the testing of donors and the recovery, processing and distribution of tissue in order to assure that human tissue is safety and effective for all transplant recipients. As drafted, the legislation is carefully designed to insure that regulation of human tissue will preserve the altruistic nature of donation.

While the risk of HIV transmission initially raised the public's awareness of the need for enforceable uniform tissue bank standards, concern about the lack of appropriate regulation has recently been heightened by reports of abuses and controversial practices by some tissue banks. One of our members has experience with a tissue bank having recovered and distributed tissue from a donor known to have tuberculosis.

There have also been reports of individuals falsifying donor records. As mentioned in previous testimony, donor tissue is being imported into the U.S., with few or no attempts to verify the donor background. There are reports of routine recovery of donors as long as 48 to 72 hours after death, notwithstanding AATB guidelines that state that no recovery shall be made after 24 hours. Furthermore, because most tissue is not subject to any regulation, there is no control over the representations that tissue banks make about the donor, the tests that have been performed on the tissue to prevent contagen or the procedures used to process the tissue.

As presented in greater detail in my prepared statement, Mr. Chairman, NTB's position on regulation of human tissue may be summarized as follows:

Human tissue is not made by man. Its supply is wholly dependent upon the willingness of donors and their families to donate tissue to others. Any regulatory scheme applicable to tissue transplantation must not only protect the public health, but must also be crafted to preserve altruism and adhere to the spirit of the National Organ Transplant Act of 1984.

Any legislation should recognize that, in this field in particular, standards should be developed by or in close consultation with the scientific and medical professionals and organizations within the transplantation community. Ultimately, such standards should be required for all tissue banks in this country, either through requiring adherence to professionally develop standards by using the Federal reimbursement system or through direct FDA regulation.

Congress must develop a means of traceability of human tissue under which all donors and recipients of human tissue may be identified in cases of potential transmission of communicable disease.

Congress should bring a halt to the existing crazy-quilt method of regulation of human tissue—sometimes as a medical device, sometimes as a drug, sometimes as a biological product and sometimes not at all—and replace it with uniform regulation similar to that now in place for blood products.

Regulation of human tissue should not be through the pre-market approval approach, which involves the treatment of clinical data as proprietary information not available to others, threatens reimbursement for transplantation and is medically unnecessary in the face of 30 years of experience with tissue transplantation.

Tissue banks themselves should be identified and registered by FDA and subjected to reasonable standards governing testing, processing and distribution of human tissue.

Mr. Chairman, it is important that NTBC clarify its position on the use of "voluntary" or professional standards to insure the protection of the public health. As you know, under S. 2908, the Secretary of Health and Human Services is required to contract with a nonprofit national council which is charged with the development of professional standards for tissue banks. These standards must be met by all tissue banks who are members of the council. If the FDA determines that professional standards are sufficient to insure safety and effectiveness of tissue, it may decline to promulgate its own standards for such tissue.

As stated in previous testimony, while most of the oversight of tissue and tissue banks has been done through accreditation by voluntary membership organizations such as the AATB, today, although such accreditation has been available since the mid-1980's, only a fraction of all tissue banks are accredited as of this date. This lack of participation in organizations with professional standards underscores the fact that a purely voluntary process cannot take the place of a sound scheme to control and standardize the quality of transplanted tissue.

While the bill as drafted does not require it, the NTBC would support an approach under which all tissue banks are required to

be members of the council, thus subjecting all tissue banks to professional standards. This could be accomplished, for example, through a requirement that is a condition of participation in the Medicare and Medicaid programs, hospitals and physicians may only use tissue from banks who are members of that council. A system like that proposed in S. 2908 would be strengthened, if enforced through a Federal reimbursement mechanism.

Mr. Chairman, allow me to emphasize the negative impact of requiring traditional pre-market approval of human tissue. Clinical trial data submitted in the support of a PMA are withheld from the public, because these data are regarded as trade secrets by the FDA. The impact of this requirement is that such data typically are not shared with others who must submit their own pre-market approval applications to gain approval of their products, in this case human heart valves that tissue banks distribute.

While this treatment of clinical data is appropriate in the commercial marketplace, its ramifications are totally inconsistent with the spirit of the National Organ Transplant Act of 1984, which prohibits the commercialization of human organs and tissue intended for use in human transplantation. There is little doubt that tissue donation could decline significantly, if donors think that their own tissue or the donated tissue of a loved one is being commercialized and sold for profit by a proprietary tissue bank.

Under S. 2908, the entire field of tissue procurement, processing and distribution would fall under a standardized approach which does not involve the regulation of one tissue at a time. Under this approach, more tissue will be subjected to standards more quickly than under the current piecemeal approach. Action by Congress would be an important step toward their protecting the public health, by regulating and controlling the quality of human tissue for transplantation, while assuring the continued availability of life-saving tissue to needy patients.

Mr. Chairman, this completes my statement and I will be pleased to respond to any questions you may have.

[The prepared statement of Mr. Sandler may be found in additional material.]

Senator SIMON. We have a vote on on the floor of the Senate right now, so we will have to take a 10-minute recess.

[Recess.]

Senator SIMON. The committee hearing will resume.

I gather—and maybe I am hearing and reading something into this that I should not—that you, Mr. Sandler, believe that there is a greater problem with tissue banks than Dr. Cuono does. Am I misreading either one of you?

Mr. SANDLER. First of all, let me say both on behalf of my own agency, Mile High Transplant Bank, which is one of the first several transplant banks accredited by AATB, we strongly support AATB. It has the only available professional standards. Our concern, as has been testified by quite a few people here, are the outliers, and although 100 banks have applied for AATB accreditation, today only 43 are actually accredited, and the actual number of tissue banks is unknown. I think that question was asked and, although there were estimates of as many as 400 in the Public Health Service study of a year ago, no one really quite knows. So

our concern is putting in a mechanism that would take away an individual tissue bank's ability to decide whether they wanted to follow standards or not.

Senator SIMON. Dr. Cuono, my staff handed me a note, but I did not realize that Dr. Gitelis has some testimony here. My original note just said you were accompanying Mr. Sandler. Did you wish to comment on that at all, Dr. Cuono?

Dr. CUONO. I think that the opinion expressed by Mr. Sandler are consonant with the use of the American Association of Tissue Banks, and basically underscored by your own preliminary comments, Mr. Chairman, that it is not a huge problem in terms of scaring the public. But we have been working with voluntary accreditation and standards for years, and S. 2908 does not, in our opinion, move ahead from that, and we have been looking for external oversight for more than 10 years and we think that is important. I think that is what I am hearing from Mr. Sandler. How the mechanism for that can be achieved could be discussed by a panel or a task force, but that is what we are really struggling for.

Senator SIMON. I apologize. We look forward to hearing from you now, Dr. Gitelis.

Dr. GITELIS. Senator Simon and members of the committee, my name is Steven Gitelis. I am an orthopaedic surgeon at Rush Presbyterian St. Lukes Medical Center, in Chicago, and a professor of orthopaedic surgery at Rush Medical College. I am also the co-medical director of the Tissue Bank at the Regional Organ Bank of Illinois and a member of the American Academy of Orthopaedic Surgeons, as well as the American Association of Tissue Banks.

I am speaking today as an orthopaedic oncologist and surgeon who depends a great deal on the existence, availability and safety of transplantable bone tissue. The goal of my practice of orthopaedic surgery is a successful outcome for patients who depend on my skills and medical judgment. As part of those skills, I am able to control only a small portion of the transplantation process, to make the proper choice of bone graft by shape and size, and to insure its proper implantation.

Excluding the tissue bank over which I have control, I and thousands of other orthopaedic surgeons are helpless to insure the proper origin, safety and efficacy of grafts. It is shocking to me, as a physician, that there are no enforceable standards to protect patients. Historically, human tissues have been utilized for transplantation experimentally and clinically for the last 50 years.

In the early 1940's, the United States Navy pioneered tissue banking in this country. For many years, the Navy operated the only tissue bank which supplied bone and skin grafts to physicians. Once research hurdles were cleared and large-scale transplantation of bone and tissue became relatively common practice, there was as proliferation of tissue banks across the country. Most of these banks were established by the orthopaedic surgeons or their departments at hospitals in which they were needed.

Several free-standing banks with no particular hospital affiliation carved out a vital niche in the community of tissue banking, by providing large numbers of grafts to surgeons working in the thousands of hospitals without their own tissue banks.

The past years have seen a growing number of organ procurement organizations recognizing the benefit of centralizing all donation and moving the old hospital-based tissue banks under their umbrellas. The vast majority of tissue banks in the United States perform their duties in an altruistic and professional manner, and many conform to the voluntary standards promulgated by the American Association of Tissue Banks.

In my view, however, resolution of concerns over disease transmission and other problems mentioned in Mr. Sandler's statement will require more than voluntary standards. Even though the risks associated with disease transmission are extremely low, even minimal risks must be reduced. You are well aware of the two cases of HIV transmission via bone grafts which have occurred in the past 3 years. Far more disturbing to me is the spread of foreign tissue into the United States, without any requirements for licensing or regulation.

We are a far cry from the era of the Navy tissue bank, Mr. Chairman. Bone and musculoskeletal tissue grafts now number close to 300,000 annually. Total transplant procedures in this country may have already totalled over 1 million. From children with scoliosis, athletes with a variety of sports-related injuries, older adults with degenerated joints, to people of all ages with fractures, defects and tumors, bone transplantation provides a method of treatment which has become routine in the armamentarium available to surgeons like myself.

The time has arrived to enact legislation such as S. 2908, which requires the establishment of uniform standards applicable to all transplantable tissue and tissue banks, in order to better insure the safety and reliability of this vital part of my practice and the practices of my colleagues across the country. Not only does this make for good medicine, but patient care demands it.

Thank you for the opportunity to address you today.

Senator SIMON. Thank you, Dr. Gitelis.

You say in your statement, "Far more disturbing to me is the spread of foreign tissue into the United States, without any requirements for licensing or regulation." I address this to any of you on the panel: Is that an increasing factor in tissue transplant today, or is it not? I guess that is the first question.

Mr. SANDLER. Mr. Chairman, as I think I stated before, I do not think we really know, because we do not know who all the players are out there. A lot of the information is anecdotal. I can tell you in the past 6 months, I have received a call from a doctor who was inquiring whether we were interested in importing tissue from the Ukraine. I asked him a lot of questions, asked him to get me some information and I never heard from him again. It tells you that something is going on.

I do not know how we get a handle on this, unless there is some type of mandatory registration, so we know who the players are and we can get an idea what really is going on within the field.

Senator SIMON. Dr. Cuono.

Dr. CUONO. I would agree, Mr. Chairman. I think that anecdotal right now is probably the most apt description. There is not a stream of evidence that any of us has seen to corroborate or support a concept that, yes, this is a major problem. It is anecdotal

and largely unknown. I think that compulsory registration of all facilities dealing with screening, acquisition, processing and distribution of tissue will identify the universe of the activity in this country and help us at least temporarily establish a ground floor with which we can work with our European and Pan Asian colleagues.

Senator SIMON. Dr. May.

Mr. MAY. Well, I can just concur with what has been already said. I mean there is not enough information, but we really do need to get that information so that we can make a sound judgment one way or another.

Senator SIMON. Dr. Cuono, if I can just use your testimony as a basis for asking questions here, do all of you agree that we should have compulsory registration of all tissue banks?

Mr. SANDLER. Yes.

Dr. GITELIS. Yes.

Mr. MAY. Yes.

Senator SIMON. The answer is yes from all three. The establishment of uniform donor screening criteria?

Mr. SANDLER. Yes.

Mr. MAY. Absolutely.

Dr. GITELIS. Yes, we need that.

Senator SIMON. I will not ask you, Dr. Cuono, whether you agree with your own testimony.

Dr. CUONO. Thank you, Mr. Chairman.

Senator SIMON. Establishment of a tracking system capable of reconciling each step of transit of all tissue from donor to recipient?

Mr. MAY. Yes, we need that and that is part of our testimony, too.

Mr. SANDLER. Absolutely. It is a real problem for the tissue banks right now. We have no way to get that information back from the transplanting surgeon, and so some outside enforcement would really help the current process.

Dr. GITELIS. Mr. Chairman, I would agree.

Dr. CUONO. May I make a comment, Mr. Chairman. In terms of tracking, the central problem, as Mr. Sandler alluded, is that in the current construct of tissue banks, they are distributing to a wide variety of intermediates. What I mean by that is they may distribute to an orthopaedic surgeon, they may distribute to a hospital central receiving office, they may distribute to a burn center, and there is no clout that the bank has in terms of getting information back on who the ultimate patient recipient is.

I may send bone to Dr. X in Illinois and Dr. X may feel that he needs to use that bone in a patient, finds during the surgery that some other procedure can be done and does not have the need for the bone. That bone may wind up in the surgeon's locker or in a refrigerator or freezer and used on another patient. I am not saying that should not be done, but we have no way of tracking that. And in the case of suspected disease transmission, it is a nightmare and that was brought to light by the Virginia incident.

I might add that, in the Virginia incident, all of the organ recipients died within 30 days of receiving their organs. One was known to be positive for HIV at the time of death of that organ recipient, but the HIV seroconversion was attributed to blood transfusion, as

opposed to a possibility that the organ itself was infected. That was in 1985.

The index case of the Virginia incident did not come to light until 5 years later, in 1990, and I think this points up the fact that the UNOS type of system, the United Network of Organ Sharing, which is designed to assure equitable distribution of the precious resource of organs to surgeons and ties in reimbursement to help with distribution, was never designed to track organs. And since there are only 9,000 organs transplanted annually, if you now look at 300,000 tissues transplanted annually, the UNOS system, which was never designed to track organs, does not have a prayer of being able to track tissues.

Senator SIMON. And as I follow your recommendation, you say, using your example when that bone marrow transplant is not used and put in the refrigerator, that there should be a tracking of that?

Dr. CUONO. Right, and there are a number of different systems that a panel could look at. One that we have discussed in our association, which would be of low cost, would involve having hospitals act as tissue distribution centers. In other words, my bank would not distribute directly to Dr. Gitelis. It would distribute to the hospital, Rush Presbyterian, where he operates, and this is no great new thing.

It is the way blood banks operate. The regional collection centers do not give me blood when I am operating on a patient. They give the blood to the blood bank at Yale New Haven Hospital, and then I request it and tracking who are you going to use it on, and there is checking back and forth. And by having tissue distribution centers within hospitals such that banks would give it to hospitals where it could have Federal oversight and also JCAHO oversight would be one model that would help this problem of tracking immensely.

Senator SIMON. Dr. Gitelis, is this too cumbersome or is this practical?

Dr. GITELIS. In actuality, that is exactly how it works at Rush Presbyterian. Now, bear in mind that I wear two hats. I am the medical director of a tissue bank and recognize tracking as an important issue, but also a surgeon who implants these tissues, so I think, as a result, we track tissues this way because it is doable, it is enforceable. But I am aware of the fact that other institutions that receive grafts, this type of tracking is not done.

Senator SIMON. Dr. Cuono has a 10-point program. I think you all heard his 10-point program. Dr. May, any reaction?

Mr. MAY. It sounded like a very good program, actually, and within the AATB, of course, we have been dealing with this issue for a long time and set patterns have developed in our response to questions of this nature, and Dr. Cuono's testimony reflects that thought process, as well as his own particular rendition of it, but I think that, in general, the ten points were very much in line with the Red Cross thinking.

Senator SIMON. Dr. Gitelis.

Dr. GITELIS. I would agree. I think it is a very comprehensive approach to the problem and I think it is a good way of thinking.

Senator SIMON. Mr. Sandler.

Mr. SANDLER. I would agree, as well. I think most of those elements are already present in the current voluntary accreditation process, but the issue continues to be enforceability.

Senator SIMON. I appreciate your testimony. We would like to follow through with all four of you, as FDA moves ahead and it appears that sometime late this fall or early this winter, we will have some concrete proposal and at that point I am very eager to get your response, too. But I think your testimony has been helpful to us here on the committee and I am sure our colleagues at the FDA feel this is helpful, too.

We thank you very much.

Mr. SANDLER. Thank you.

Mr. MAY. Thank you.

Dr. CUONO. Thank you, Mr. Chairman.

Senator SIMON. Our final panel is Steven G. Anderson, President of CryoLife Cardiovascular, Inc., of Marietta, GA, and Dr. Richard A. Hopkins, Director of Pediatric Cardiac Surgery, at Georgetown University Medical Center.

We are very happy to have both of you here. Dr. Hopkins, since you are sitting in that first seat, we will call on you first.

STATEMENTS OF RICHARD A. HOPKINS, M.D., DIRECTOR OF PEDIATRIC CARDIAC SURGERY, GEORGETOWN UNIVERSITY MEDICAL CENTER, WASHINGTON, DC; AND STEVEN G. ANDERSON, PRESIDENT, CRYOLIFE CARDIOVASCULAR, INC., MARIETTA, GA

Dr. HOPKINS. Thank you.

Senator Simon and members of the committee, my name is Richard Hopkins. I am Director of Pediatric Cardiac Surgery at Georgetown University Hospital, and hold various administrative positions with the American Association of Tissue Banks, LifeNet Transplant Services, and actively pursue basic medical research related to human heart valves.

However, I speak to you today as a clinical cardiac surgeon who specializes in reconstructive cardiac surgery. While I treat many adults in my practice, I treat an even larger number of children. Thus, I would like to specifically address the effect of tissue regulation on pediatric cardiac surgery.

Despite the efforts of many cardiac surgeons and against the advice of their own physician scientist advisory panel, the FDA has, nevertheless, chosen to require pre-market approval of human heart valves, an undertaking that will have serious adverse consequences for patients, especially children, in need of heart valves.

In my opinion, Federal regulatory policy should attempt to preserve altruism in tissue processing and stimulate advances in tissue processing. FDA's current approach will not protect public health, because it will take decades to implement.

Allograft valves were made and designed by God. From an engineering standpoint, they are the most prefect implant we have. Because the valves are natural, there is optimal hydraulic flow and hemodynamics, even where size constraints are imposed either by the size of the patient or by the nature of the cardiac reconstruction.

Moreover, since each prototype already has functioned properly in the donor, there is superior hemodynamic performance. Recipients of human allograft valves do not require anticoagulation therapy, since the incidence of thrombo-embolism and hemolysis is extremely low. This is especially important, since children do not respond well to coumadin, the anticoagulant drug that is prescribed for mechanical valve recipients. Such anticoagulants also are contraindicated for women of child-bearing years.

Implantation of human heart valves is relatively easy. Infections following implantation of human valves occur less frequently than with other substitutes, and the human valve has much greater resistance to endocarditis than mechanical or porcine valves. Catastrophic failures that can occur with mechanical valves are almost nonexistent with human valves.

Most important, the expected life of the human replacement valve is substantially longer than that of the porcine or mechanical substitutes. They resist wear for a long time and reconstructions can be achieved that allow the child to "grow into" his adult size replacement. By contrast, children who receive a porcine valve usually need to have the valve replaced every 2 to 4 years, due to calcific degeneration. In addition to the obvious pain and discomfort, with each operation, there is an average 5 percent mortality.

In sum, the general medical consensus is that human allograft heart valves are substantially superior to other substitutes for most pediatric patients in reconstructing the outflow tract of the right ventricle, for women of child-bearing years, for infected aortic roots and for various complicated reconstructions.

These specific patient subgroups must have access to human heart valves. While there are often indications for porcine or mechanical valves in patients—and I use all of them—cardiac surgeons should certainly not be limited by the FDA to the use of only manufactured valves.

I am certain that most cardiovascular surgeons support a regulatory mechanism designed to learn more about the nature of tissue processing and assure that processing is of the highest quality. However, classification of human heart valves as "experimental" medical devices, while perhaps appearing to be a simple regulatory approach, does not make any sense, in light of the fact that the safety and effectiveness of these human replacement valves has been well documented over the past 20 years and has never really been seriously challenged. It is not necessary or appropriate to regulate very tightly that which man did not make.

I would urge you to pursue the regulatory approach that is taken by S. 2908, which makes all transplanted tissues subject to standards based on meaningful scientific evidence. In the meantime, regulation of implantable human tissue as a medical device should be stopped. If it is not and the shortage of allograft valves results, children will suffer real pain, be subjected to multiple unnecessary surgeries, have less optimal surgical reconstructions, leading to greater number of complications and deaths.

Thank you.

[The prepared statement of Dr. Hopkins may be found in additional material.]

Senator SIMON. Thank you. Let me also thank you for coming to a meeting in my office some months ago with Dr. Kessler. I think that meeting helped move us in the right direction. I think we are groping a little bit, but I think we are heading toward some solid answers in this field, and I want to thank you personally, Dr. Hopkins, for your willingness to take time out to be part of that process.

Dr. HOPKINS. Thank you.

Senator SIMON. Mr. Anderson.

Mr. ANDERSON. Good morning, Mr. Chairman.

My name is Steven Anderson, and I am the President and cofounder of CryoLife, Inc., of Marietta, GA. I am pleased to have the opportunity to share some of our views on tissue and organ regulation with you.

In the interest of time, I wish to limit my remarks this morning, but would like to submit my complete statement for the record. Let me begin with some background on CryoLife.

We were founded in 1984 and we process and preserve human cells and tissues for transplant. CryoLife does not procure tissue nor does it own the tissue that it preserves. It provides services to 139 organ and tissue banks throughout North America and Europe. CryoLife's specialty is ultra-cold preservation of human heart valves, and since 1984, over 900 physicians at 350 medical centers in the United States have implanted more than 12,000 CryoLife valves. We think that this may be the largest series of allograft valves in the world. The majority of these valves have been used to treat children with congenital heart defects. Even so, we know that a great deal remains to be learned about allograft tissue.

Tissue preservation as a science is still in its infancy. For example, right now, we are testing a solution for viral inactivation that we call GIP that kills yeasts, bacteria, fungi and perhaps even the AIDS virus on contact, without harming the tissue. If our testing works out as we hope, the viral inactivation process will make better, safer valves, bone and other tissue.

We also preserve other tissues for transplant, including human veins, bone and connective tissue. Our vein, for example, is used in coronary bypass when the patient's own vein is not available, and in peripheral vascular reconstruction, which can save limbs that might otherwise be amputated.

Funded by the National Institutes of Health, the U.S. Navy and CryoLife's own investment, we continue to work on both better methods of preservation and on new applications of our existing technology.

I would like to turn to some of the regulatory issues before this committee. There is no question in my mind that organ and tissue transplantation should be regulated. Discussion of tissue regulation is often coupled with discussion of infectious disease transmission, and the Public Health Service Task Force on Organ and Tissue Transplantation found that the risk of tissue related disease transmission is relatively small. Still, it has happened in the past and we must take all reasonable steps to make sure that it does not happen again.

Regulation can also ensure that only safe and efficacious tissue is transplanted. Tissue in its natural state is perfectly designed for

its natural function. But transplantable tissue may well have been dissected, transported in an artificial solution, bathed in antibiotics, irradiated, frozen, stored, thawed, packaged and transported again. There is a lot of room for error, if the process is not carefully designed and executed.

A third reason for regulation is that it imposes a valuable discipline on even the most careful provider. There is no question that our preparing the heart valve IDE has improved CryoLife's processing. For example, compliance with good manufacturing practices has improved the uniformity and quality of the tissue we preserve, as well as our recordkeeping capabilities.

I think that, collectively, we have really gone beyond the question of whether regulation has value. The issues now are who should oversee the regulatory system, what kind of regulation will get the job done most effectively, and what is an appropriate time frame for putting a system in place.

As to the first question, who should oversee the regulatory system, I firmly believe that the FDA is the only appropriate choice. The issues are important health and safety questions and they deserve FDA attention. FDA has both the experience and credibility, as well as a nationwide presence to enforce its regulation.

I do not believe that a system that gives primary regulatory authority to the tissue banks themselves can be effective. This industry is too large and too diverse to come together under a voluntary scheme.

Let me turn to my second question: What kind of regulation is appropriate? In entrusting FDA with the responsibility for regulating drugs, devices and biologics, Congress has provided it with a full range of regulatory tools, and I believe that we should have their full range of regulatory tools available in regulating human tissue.

Whatever regulatory scheme is chosen, it must provide a quick way to review and sign off on changes in the way things are done. Tissue engineering is a science that is moving very rapidly. Five years from now, our processes will look very different from today. We cannot afford a regulatory process that stifles innovation and creativity.

Finally, what is an appropriate time frame for putting a system in place? There are over 300,000 transplants of human tissue in the U.S. each year. There are more tissue transplants per year than there are heart pacemaker implants. The time to regulate the industry is now.

One thing that the FDA could and should do very quickly is to write regulations for preventing transmission of infectious diseases. Minimally, these should mandate the most advanced donor screening, a consistent tracking and recordkeeping system, and whatever system we choose, we should not paralyze FDA while it is being implemented. In a crisis, someone must have the legal authority to remove a dangerous product from the market.

All of the things I have described above are things that FDA already has the statutory authority to do, and I believe, heart valves notwithstanding, that the FDA has the authority to do them in a way that does not disrupt the tissue community or jeopardize the availability of life-saving tissues. And that is not to say that the

current way is the only way, and I do not reject the legislation out of hand. For one thing, I recognize the very real resource limitations that FDA faces, a problem that may require congressional action. Is it not less costly to provide FDA with the funds necessary to regulate tissue, than to legislate a new and completely separate regulatory entity? It is worth remembering that the FDA's regulatory system has stood the test of time.

Thank you.

[The prepared statement of Mr. Anderson may be found in additional material.]

Senator SIMON. I thank you.

You touch on the need at FDA for additional personnel. There is just no question that there is a need, and it is something that we ought to be addressing.

Both of you heard Dr. Cuono's 10-point program. Any reaction to that, Dr. Hopkins?

Dr. HOPKINS. I think the general theme that you are hearing today from everybody is that we are all pro-regulation, and I think the kind of scheme that he outlined was very good. I think the points that other people have made, there has to be some teeth in it, there has to be Federal involvement, it cannot be just voluntary, are very, very appropriate.

I think the concerns are the exact nature of the regulatory impact and trying to fit round pegs into square holes, and I think that is the way I hear the theme, and I have no disagreement with the general theme of those 10 points.

Senator SIMON. Mr. Anderson?

Mr. ANDERSON. I read over those 10 points while I was seated in the audience and I do not have any problems with any of them and support them.

Senator SIMON. Dr. Hopkins, do you find you get quality heart valves now? I assume you have to examine each heart valve when you get it. Do you occasionally or frequently have to send it back, saying this is not appropriate or this is not quality enough for my patient?

Dr. HOPKINS. I have personally done over 200 allograft cardiac valve implantations in the last 7 years. I have never had to return a valve because it did not meet surgical standards.

Also, like Dr. Gitelis told you, I only get my tissue, as he does, from facilities which meet all of the most rigorous AATB-type standards, so I am very confident about the quality of the tissue.

I think it should be pointed out, although we are very concerned about infectious disease transmission, the index cases that we are talking about do not involve cardiac valve tissue. There has been no documented case of HIV transmission by allograft cardiac valves.

Senator SIMON. But if we are not careful——

Dr. HOPKINS. No question, we should have in place mechanisms for tracking, mechanisms for screening, and mechanisms for looking at methods for disinfecting the tissue. All of that really must be done.

Senator SIMON. And when you say you deal only with the most reputable or those with the highest standards, by implication you

are saying there are some that do not maintain the highest standards, or am I reading something into that?

Dr. HOPKINS. You may be reading a little bit more. I have found it effective just to deal with a couple through the AATB network mechanism. I share some of the concerns that I am sure are out there, things that are being done with tissue that we would not want to be done. I personally have not seen it. I have never been approached by people dealing with tissue and that sort of thing. I am sure it could occur and that is why these kinds of laws and rules should be established.

Senator SIMON. Mr. Anderson, you get a more overall look at this thing. In terms of your firm, the tissue banks you deal with, would you say they are all following the highest standards?

Mr. ANDERSON. Yes, I would. We work very closely with the tissue banks that send tissue to us for preservation. We assist them in the training of their staff as to how to properly procure the tissue and package it in proper solutions. Since we have been doing that, the quality of tissue that we have been receiving has substantially improved.

Senator SIMON. Dr. Hopkins, just as general background for me, in talking about the human heart valves, you say they resist wear for a long time and reconstructions can be achieved to allow the child to grow into his adult size replacement. Say an 8-year-old gets a heart valve, then that is replaced once or twice or periodically during that person's life?

Dr. HOPKINS. If you choose for that child a mechanical valve, there are size constraints. It is a fixed rigid prosthesis, so that not only will you have to anticoagulate the child, which means he cannot participate in any kind of sports, any kind of activities other than walking, that valve will become too small for that child as he grows and will have to be replaced for size constraints alone.

If you were to pick a porcine valve or a pig valve, you would have fairly similar size constraints, but you would not have the requirement of anticoagulation, but that valve calcifies in the human circulation, particularly in children who have a very rapid calcium turnover with bone metabolism, so essentially that child will come back with an obstructive valve in 2 to 4 years.

When the child is about 15 kilograms or around 30 pounds, in most positions in the heart, we can reconstruct with an adult-size valve, so that for size constraints alone, the child would never require another valve replacement.

Senator SIMON. And of the 200 operations that you have done, how often have you had to later do another operation?

Dr. HOPKINS. In those 200, I have got one patient who I have had to replace the allograft valve with another allograft valve and I have another patient who has, at about 5 years after implantation, some rigidity and calcification forming in the leaflets, and I suspect that child will come to re-replacement sometime in the next few years. So that is two out of 200.

Senator SIMON. We thank both of you. Let me express my thanks to all the witnesses. I think we have had a constructive hearing. I think we are making some progress. I think we are going to end up with something that will be a good product.

Again, I would like to say to the two of you, that when we get to a specific proposal from FDA, we would appreciate your counsel and your reaction to that.

[Additional material follows.]

PREPARED STATEMENT OF MICHAEL TAYLOR

Mr. Chairman, I appreciate the opportunity to be here today to discuss the regulation of human tissue products and your bill, S. 2908, the "Human Tissue Transplantation Act of 1992." With me today are Ann Wion, with the Department's Office of the General Counsel; James Weikel, with FDA's Office of Health Affairs; and Gordon Johnson, with FDA's Center for Devices and Radiological Health.

We at FDA and the Public Health Service are currently evaluating how best to ensure that the public health issues posed by the growing therapeutic use of transplanted human tissue are properly addressed. We are engaged in discussions with various tissue banking entities, professional organizations, and other interested parties, to learn more about the issues and how they might best be addressed. We would like to share with you today some of what we have learned, focusing on the questions we believe must be addressed in considering any new regulatory scheme for tissues.

Let me say at the outset, though, that we appreciate your initiative in introducing S. 2908. This is a critically important area that deserves our thoughtful consideration. We look forward to working with you and other members of the committee to be sure that our Federal regulatory efforts serve the public health in the most efficient and productive way.

Background

FDA has been involved in the regulation of human tissue products for some time. Our Center for Biologics Evaluation and Research has been regulating blood for decades under the authorities of

the Public Health Service (PHS) Act and the Federal Food, Drug, and Cosmetic (FDC) Act. Other tissue-derived products, such as human hormones, have also been regulated as drugs and as biologics. Transplanted human tissue may also be subject to regulation by FDA under the 1976 Medical Device Amendments, and several categories of human tissue are being regulated as medical devices. These include corneal lenticules (corrective lenses derived from corneal tissue and applied to the cornea), which are considered to be a post-amendment device requiring premarket approval; dura mater allografts (brain membrane material), which have been recommended for classification by an advisory panel; and heart valve allografts, which are replacement heart valves and subject to the 1987 regulation requiring premarket approval applications.

While FDA regulation of human tissue is not new, developments in recent years have prompted the Public Health Service and FDA to take a fresh look at our regulatory tools and practices. One important development has been the rapid technological progress in the field of tissue transplantation, which has greatly expanded the actual and potential uses of human tissue for important therapeutic purposes. This progress is positive and exciting because of the benefits it has delivered and promises to deliver to patients. I want to assure you that FDA recognizes and values those benefits and takes them into account as we do our regulatory work.

As the use of tissues has expanded, however, we have become increasingly aware of public health issues that need to be addressed. One of these developments, of course, is the possibility of HIV and other infectious disease transmission. Another is the increasing use of innovative processing techniques for tissues that expand the range of potential uses but also present questions about whether the processing technique affects the safety or utility of the tissue.

Our current review of tissue regulation is intended to determ the proper role for Federal oversight in assuring that these questions of tissue safety and utility are adequately addressed.

Infectious Disease Transmission

The discovery in 1991 that seven people had been infected with the HIV virus through transplantation of organs and tissues from a seronegative donor sparked discussion within the tissue bank community and the Public Health Service of how the risk of infectious disease transmission could be reduced. A PHS Task Force was convened and, in July 1991, forwarded a report to the Assistant Secretary for Health James Mason that assessed the role of the Federal government in protecting the public health from infection associated with organ and tissue transplantation. That report found that organ and tissue transplantation procedures were addressed by a variety of controls under Federal law, state law, and voluntary industry standards. Although the Workgroup found the risk of HIV infection to be quite low, the Workgroup recommended that PHS revise its guidelines on donor screening and record keeping. To address concerns associated with the reliance on voluntary industry standards, the report recommended a more extensive continuing evaluation of the need for additional Federal regulation in the tissue transplantation area.

On October 16, 1991, the PHS working group held a public hearing in which 28 organizations or individuals participated, most of which supported at least some baseline of Federal regulation to assure safety.

On December 12-13, 1991, a meeting was held at the Centers for Disease Control (CDC) to develop a consensus on the content of a revised PHS guideline, relating to donor screening and testing and recordkeeping, to minimize the risk of infectious disease transmission.

The PHS Workgroup submitted a second report on August 5, 1992, to Assistant Secretary for Health, Dr. James Mason, recommending at least a mandatory "regulatory floor" consisting of registration of tissue banks, donor screening criteria, and recordkeeping to track tissues. The group recommended that these requirements be administered by FDA, but stressed the need to assure the availability of adequate resources before commencing any new program. The group also noted an array of safety and effectiveness issues beyond the risk of infectious disease transmission that should be evaluated.

In the meantime, much has already been accomplished to minimize the risk of HIV transmission. Guidelines on donor screening and testing are being revised by PHS. Finally, voluntary accreditation organizations, eye banks, and tissue banks have responded vigorously to the need for donor screening, recordkeeping and tracking of tissue recipients.

Based on the voluntary measures currently in place, we believe the risk of HIV transmission associated with human tissue transplantation is very low. I must note, however, that the risk of HIV transmission can never be reduced to zero. Although most potential donors can be rapidly screened and evaluated for the presence of disease, there is a latency period between acquisition of the virus and positive test results. In the event that a donor is in that relatively short window period, no test conducted at the time of donation will detect the presence of virus. Indeed, this is the reason that tissue banks have instituted other donor screening criteria, similar to blood banks, to minimize this risk.

Current Practices in Tissue Transplantation

The technology of tissue transplantation has developed dramatically over the last decade. As a result, many human tissues, such as bone grafts, tendon grafts, corneas, nerves, and

skin grafts, have become an integral part of medical procedures. As tissue transplantation practices have grown, so has the number of individuals and institutions which collect, process, and provide these materials, and so has the need to address questions of safety, product quality, and the maintenance of the tissue's utility.

When fresh human tissue is recovered and used immediately in a patient in need without any processing, there are few questions about potential harm from processing fluids or about whether tissue viability and effectiveness have been maintained. But modern tissue banking has become much more sophisticated than that. Refinements in technology have permitted treatment of tissues with various chemicals, antibiotics, and nutrient solutions to maintain functionality of the tissue for a longer time period. Cryopreservation technology permits tissue storage at very low temperatures nearly indefinitely. Packaging containers designed to permit aseptic deep freeze storage have been developed. Tissue transplants are shipped in special containers. These preservation, storage and transportation technologies have permitted storage and national distribution of tissues previously managed locally and in a short time frame.

Each of these interventions raises questions, however, as to whether the initial safety and utility of the tissue has been preserved -- questions similar to ones FDA has traditionally addressed regarding medical devices, unapproved drugs or biologics, or other medical products.

Heart valve allografts are an example of this phenomenon. As medical practice and technology evolved, human heart valve tissue was subjected to a variety of new processing techniques, but there was little consistency or common understanding of the best processes. For instance, after heart valves are recovered, they are immediately placed in a solution which contains various chemicals including nutrients and up to five different

antibiotics. Over time, some heart valve processors had modified the mix of antibiotics after finding that certain ones were too cytotoxic and resulted in damage to the valves. However, not all processing centers adapted to such new information as it was developed. Further, not all processing centers were uniformly requiring state-of-the-art donor screening and testing for the allograft tissue materials.

FDA Regulation of Heart Valve Allografts

FDA has used its authority under the Medical Device Amendments 1976 to address the safety and product quality (or utility) issues posed by heart valve allografts. FDA has called for more standardized approaches to heart valve processing and for the generation of data validating optimal approaches to assuring the safety and quality of the tissue. FDA has taken these actions under the provisions of the 1976 Amendments that authorize FDA require "premarket approval" -- a form of individual product license -- for higher health risk medical devices (Class III devices) that were in use before 1976.

We at FDA know from long experience in both the pharmaceutical and medical device areas that imposition of such regulatory controls on products that have well established therapeutic roles can be disruptive and inevitably imposes costs. In the case of heart valve allografts, we have taken steps to achieve the goals of standardizing and validating the new processing technologi while maintaining continued access to this critical life saving tissue. We have extended the effective date for the requirement that valves be covered by investigational device exemptions to allow time for the many medical centers involved to make the necessary arrangements. We have worked with the Health Care Financing Administration (HCFA) to assure continued Medicare and Medicaid reimbursement for allograft valves -- in the interest of maintaining availability and public access to them based upon their clinical benefits to identifiable subpopulations.

While FDA intervention on heart valves has certainly imposed some costs, we believe it has also conferred significant benefits for patients, in the form of improved and more widely observed procedures for donor screening and tissue processing and handling. We are committed to working with the tissue bank and medical community to assure that access to heart valves allografts is maintained as we enhance the scientific underpinnings for their continued use.

Future Tissue Regulatory Considerations

These developments in the field of tissue transplantation and our experience with heart valve allografts, raise important questions about the proper role for and the best approach to Federal regulatory oversight. The challenge is particularly acute in devising a sound approach to the retrospective application of standards to tissues and practices that already are established in clinical practice, especially when one considers the diversity of transplanted tissue products and the vast number of such materials that are in current use.

The ideal goal, of course, is to maximize the safety and effectiveness of transplanted tissue materials, in light of improving technology and increasing patient benefits, while preserving the benefits already achieved and not significantly disrupting the continued market availability of needed products.

We are considering this issue and will be reporting on various options to Assistant Secretary Mason in November. I would like to identify some of the questions that must be answered.

We have organized our thinking around three broad questions: Is there a need for a comprehensive Federal program instead of the case-by-case application of FDA's medical device or biologics authority? If there is a need, should it be addressed under

current law or through new legislation tailored to tissues? And, finally, what would be the appropriate elements of a regulatory scheme for tissues?

First, is there a need -- a public health rationale -- for Federal intervention beyond what FDA is doing now? Certainly, reducing the risk of infectious disease transmission is one possible justification for a broader Federal role, but is the risk of HIV and other disease transmission already being adequately addressed? Is there a need for legally enforceable standards to address this risk?

Beyond disease transmission, are there other safety issues posed by current and emerging methods of sterilizing, processing, and storing tissues as they affect long term tissue reliability or performance? Beyond safety, are there issues of clinical utility that need to be addressed systematically through Federal regulation?

The answer to these questions will help us understand the potential benefits of Federal regulation and whether there is an adequate public health rationale for broader Federal intervention.

In considering a potential new legislative scheme -- the larger picture before Congress and society at large -- there are other considerations, such as the costs of the system weighed against its benefits. There are certainly direct economic costs in terms of government resources required to devise and implement a new regulatory program and the costs of compliance incurred by those who are regulated. How great would these be?

There also may be less obvious costs if, for example, a system that was not well calibrated to the task at hand interfered with

access to a product that, on balance, provided a net benefit to patients. Can Congress identify and measure these costs? And can they be minimized in any new system Congress develops?

If we conclude there is a legitimate need for a more comprehensive approach to tissue regulation, the next broad question is whether it should be pursued through such a new system or under FDA's current statutory authorities. FDA has authority today under the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act to mount just about any regulatory intervention one might reasonably consider appropriate. This is especially true since the 1990 enactment of the Safe Medical Devices Act, which enhanced FDA's flexibility in managing the introduction of products into the marketplace and expanded the agency's post-marketing surveillance and data gathering authorities.

The existing legislation was not written, however, with the full range of transplantable tissues specifically in mind, and some have suggested that, even with some of their emerging similarities, tissues are sufficiently different from conventional medical products that their regulation should be based on specially-tailored legislation. What attributes of tissues, if any, justify a new legislative scheme? Does current law fall short with respect to these attributes?

We should also ask whether there are features of the tissue transplant community itself that justify a different approach to regulation and a new statute. Is it relevant that many tissue banks are non-profit and that the source of supply relies on voluntary donations of tissues? Are there private entities or mechanisms in the tissue community that can play a role in regulation that is not contemplated by FDA's current statutes?

The last broad question to be addressed concerns the appropriate elements of a regulatory program. The regulatory tools available to FDA to regulate the broad range of therapeutic products -- including drugs, biologics and medical devices -- fall into five categories. They are (1) registration of facilities and products; (2) inspection of facilities and other enforcement mechanisms; (3) setting technical standards governing such product safety and quality-related matters as manufacturing, processing, storing, and distributing the products; (4) regulatory standards and procedures to assure the effectiveness of products; and (5) oversight of the investigational process and market entry for new products.

One strength of FDA's current statutory authorities for medical devices and biologics, from the agency's vantage point, is that they provide FDA with all of these tools, but the manner of their application properly varies from product to product, depending on the nature of the safety and efficacy question presented by a particular product or category of products.

FDA's preliminary view regarding tissues is that any Federal intervention should be tailored to the nature of the issues posed by particular tissues or categories of tissues. We think any new system that is not flexible enough to recognize the differences among tissues could do more harm than good.

But, to be credible, any regulatory regime for tissues also must consider costs imposed, as well as, satisfactorily address the issues of (1) safety, including prevention of disease transmission; (2) standards to assure product quality and utility; (3) how new processes and tissue uses, including proprietary ones, are to be handled; (4) how to build on the role of private standard setting and oversight bodies; and (5) enforcement.

S. 2908

S. 2908 addresses many but not all of these questions. Importantly, the bill recognizes the knowledge and experience that reside in the private sector. We also are exploring creative ways to harness that expertise.

S. 2908 also recognizes the role that standards may be able to play as at least a partial surrogate for individual product licensing. We are very interested in exploring this approach.

Conclusion

As these brief comments have made clear, S. 2908 does not address all of the issues, but we welcome it as an expression of interest, initiative, and willingness to explore new solutions. I thank you, Mr. Chairman, for the opportunity to present the FDA's views. I look forward to working with you to develop answers to the questions before us and to develop an approach that will assure that patients continue to benefit from the advances we have seen in tissue transplantation. My colleagues and I will be happy to answer any questions you may have at this time.

PREPARED STATEMENT OF S. RANDOLPH MAY

Good morning Senator Simon, ladies and gentlemen.

My name is Randolph May, and I am National Head of Tissue Services of the American Red Cross. As such, I speak for the 31 American Red Cross Regional Tissue Services in 22 states. I was a founding member of the American Association of Tissue Banks, and I presently serve as the secretary and member of the Executive Committee for the Board of Governors of that Organization. I am also a past president of the International Society for Cryobiology.

I welcome the opportunity to testify today before this committee on the subject of human tissue transplantation. It is estimated that more than 10,000 tissue donors annually supply more than 500,000 pieces of tissue for transplantation into our fellow Americans suffering from disease and trauma. The rapid growth of this very effective medical treatment requires that there be increased scrutiny to protect the American public from diseases which might be transmitted via tissue. The American Red Cross strongly believes this may be accomplished by (1) registration and licensing of tissue banks, (2) establishment of tissue-specific donor screening procedures, and (3) the use of fail-safe procedures to link donors and recipients in order to track potentially infectious tissue.

We wish to thank you, Senator Simon, for your concern over this issue, and your organization of these hearings to bring the facts to the American public.

The American Red Cross began providing tissue services in 1984 by undertaking much needed procurement, processing, storage and distribution of human tissue throughout the United States. We supply human bone, heart valves, veins, skin, tendons, and cartilage for transplantation, so recipients can walk, hear, and recover from burns and trauma. Our Regional Tissue Services range geographically from Connecticut to California and from Minnesota to Texas. The Senator may be familiar with one of our original programs located at the Heart of America Red Cross Chapter in Peoria, Illinois. This past year our system supplied approximately 45,000 pieces of tissue to individual Americans for the relief of disease, trauma, and suffering. This effort represented an estimated 20 percent of all transplantable tissue utilized in the United States, excluding corneas.

In my testimony today, I would like to point out the differences between transplantable tissues and organs. There are obvious distinctions between the two types of material, both in how they are obtained and in the financial aspects of their procurement, processing and distribution. Organs are obtained in limited numbers from beating-heart, brain-dead donors. These require intense procurement efforts by 69

designated organizations. These organ procurement agencies have been established by governmental mandate, and operate as territorial monopolies. The procurement and use of organs is tightly controlled by physicians, and constitutes a specialized form of medical practice. All organs are used in life-saving procedures.

In contrast, tissues are procured from a broad array of acceptable donors by at least 100 and possibly as many as 400 diverse tissue banking establishments. At least one-half million tissue grafts are made available each year from these efforts. In contrast with organs, these tissues are processed and stored for potentially long periods of time, and are usually used in patients for life-enhancing, rather than life-saving, medical procedures. The exception is heart valves, which are often used in infants to repair congenital defects or in adults as a replacement for infected or failed valves. Both uses are life saving procedures.

Immediately then, one can see that there might be some differences in donor screening criteria and testing between organs and tissue: organ donors can be custom-selected by the physicians heavily involved in the program, taking into account the life-threatening needs of the recipient patients. Transplantable tissues, because of their typically non-life threatening clinical applications, should be required to pass much more stringent donor selection criteria, since the recipient patients will not accept any risk of HIV transmission associated with only a life-enhancing tissue transplant. Indeed, tissue banks can afford to be more selective, because of the larger number of potential donors. Another difference is that of timing. While organ transplantation has a restricted time frame for donor testing, tissue banks have a more extended time frame, because of low temperature tissue storage, in which to undertake more extensive testing.

The remainder of my testimony is guided by several principles. First, that human tissue provided for transplantation must be safe and that any required regulation of tissue must increase quality and safety. Second, that the American Red Cross feels strongly

that appropriate, enforceable standards are needed to ensure the safety of the people who depend upon transplantable human tissue to sustain or improve the quality of their lives.

Currently there is very little regulation of tissue and tissue banking in this country: only four tissues are currently regulated by the FDA. As a voluntarily self-regulated industry, tissue banking has served the public well, and has provided safe, quality tissue for the past two decades. The reported incidents of infection attributed to tissue transplantation have been rare. However, there is some cause for concern.

Last year, America experienced a major scare when an organ-and-tissue donor was suspected of transmitting the AIDS virus to seven transplant recipients (three organ and four tissue recipients). Indeed the total public harm could have been much worse since over 58 individuals received organs and tissue from this one donor. Fortunately, the tissue was obtained and processed according to current standards by one of the most respected tissue banks in the country. That tissue bank's processing methods for preparing most of the tissue from that particular donor prevented the transmission of disease. Additionally, that tissue bank has been accredited by the American Association of Tissue Banks (AATB), which currently provides voluntary standards for tissue banks and operates an inspection and accreditation program. However, without enforceable standards, there is a virtual certainty that disease transmission will occur again with tissue supplied by a tissue bank that has chosen to ignore the voluntary AATB standards.

This recent transmission of HIV infection by tissue, coupled with the increasing numbers of tissues being recovered, has caused concern within the Congress, the FDA, and the public, as to whether the current level of governmental regulation of tissue is appropriate at the current time.

For these reasons, the American Red Cross urges Congress to establish a public law that requires enforceable regulations with the specific aim of preventing the

transmission of diseases such as AIDS and hepatitis through tissue transplantation. The American Red Cross agrees with the American Association of Tissue Banks that a mechanism is needed to require licensing of tissue banking organizations, to establish tissue specific donor screening criteria, and to provide for effective and rapid tracking of tissue between donors and recipients.

Effective donor screening, including infectious disease testing, and effective tissue procurement practices are the most important ingredients in the prevention of disease transmission. The American Association of Tissue Banks, currently recognized as the professional standards- and procedures-setting organization for tissue banking, has established donor suitability requirements. Compliance with its standards is voluntary. Only 45 of a possible field of 400 tissue banks in this country have been inspected and certified to be in compliance with those standards. This leaves 90 percent of the U.S. banks uninspected and unaccredited even on a voluntary basis. This represents a significant risk to the health of the American people. Moreover, there is no effective mandatory enforcement, because if a tissue bank knowingly transgresses the standards, the "decertification" by AATB is not always a sufficient inducement to keep the standards enforced.

Tissue banks should be required to obtain a license to operate after they have demonstrated compliance with all requirements. Conversely, this license would be revoked if a tissue bank was found to be operating outside of required regulations.

In the important case of tracking donors and recipients, the process is relatively more simple in the case of organs because they are transplanted immediately after recovery and because only a limited number of organs can be recovered from a given donor. In the case of tissues, which can be banked, a long time may pass between recovery and transplantation, exacerbating the difficulty in tracking tissue during a recall or look-back procedure. More importantly, literally hundreds of pieces of tissue may be obtained from a single donor, so hundreds of recipients could be involved in a tracking

procedure. These points underscore the difference between organs and tissues, and suggest that different regulatory approaches might be needed for the two items. State departments of health and the Centers for Disease Control currently serve this tracking function well. However, communication between organ procurement organization and tissue banks regarding the notification of infection in tissue recipients needs to be specified in federal regulations. The alternative of using a hospital-based tracking system similar to blood banking is also attractive.

The regulation of tissues, including licensure, imposition of uniform donor screening standards, and trackability of tissue between donor and recipient can be minimized by utilizing the role of existing agencies of the Department of Health and Human Services. If this simple solution is chosen, then the major factors in the cost of regulation will be rule making, protocol writing, and research into the cost and infection rate associated with tissue. The benefits of such regulation would be a heightened perception of safety in the public mind and a promotion of the type of well-regulated tissue bank that would be less susceptible to failures which cause medical misadventures.

The final issue relates to the current regulation of heart valves as class III medical devices. As a class III medical device, an Investigational Device Exemption (IDE) must first be filed and then a Pre-Market Approval (PMA) submitted, yielding an extended, costly process for both tissue banks and for the FDA. In the interim, supply of and reimbursement for the tissue may be compromised.

Several issues present themselves. First, all tissues have certain elements in common. They are obtained from human donors under a set of specific selection criteria. The biofunctional use of each type of tissue is common to all configurations of that tissue. Surely an unstirred allograft heart valve or a shaped and folded piece of dura mater are not manufactured in the same sense as a captive-disc mechanical heart valve. Finally, tissue is not an investigational device or material. To cite a single example, the medical literature of transplantable human heart valves begins in the 1960's and consists of hundreds of papers detailing processing, use and outcome. Allograft heart valves are

successfully used in 5,000-10,000 patients per year. I am holding up two books which review all of this medical progress.[1]

Certainly, allograft heart valves are not experimental devices about which we need proof of safety and effectiveness before they can be used as part of normal patient care. The classification as a class III medical device and the IDE/PMA process now required by the FDA for human allograft heart valves is time consuming and costly, and should be reserved for "new" medical devices, not for items that have been used safely and effectively for approximately 20 years. Placing allograft heart valves in class III and requiring IDE's for them will make them investigational "products," thus allowing some third party payers to refuse to cover the expense of the implant. In such a case, if the patient desperately needing a heart valve transplant to save his or her life is neither covered by Medicare, nor wealthy enough to pay the $40,000-$60,000 required, then they will be denied the opportunity to obtain a heart valve and will die. Moreover, the lack of reimbursement to the non-profit providers of heart valves may cause them not to be able to supply this precious resource, half of which is used in pediatric patients.

An adequate solution to the heart valve regulatory dilemma might be for the FDA to classify these valves as class II medical devices. In this way, the FDA would still regulate their procurement and processing, there would be no IDE requirement (which is redundant anyway), the lack of third party reimbursement would be solved since class II devices are reimbursed, and the appropriate level of good manufacturing practices (21 CFR 820) would be applicable to the processing of the heart valves. This appears to be the simplest, least costly, and most effective solution to the difficult situation in which we all find ourselves in today.

These issues illustrate that while the FDA has been appropriately carrying out its assignment in regulating tissue according to its normal procedures, these may not be flexible enough for the needs of a diverse tissue field. Yet in the "Tissue and Organ

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[1] Yankah, A.C., *et al.* "Cardiac Valve Allografts 1962-1987". New York, Springer-Verlag. 1987. Hopkins, R.A. "Cardiac Reconstruction with Allograft Valves". New York, Springer-Verlag. 1989.

Transplantation Assessment Report" of July 18, 1991, by the Public Health Service Workgroup, it states that "FDA...should proceed with their pending regulations... as expeditiously as possible." If the FDA is to regulate tissue, then, it would be quite beneficial for that agency to develop a rational approach to tissue regulation that could be used to solve some of the aforementioned objections.

In conclusion, there is justification to maintain the federal regulation of human organs, tissues, and cells by the agencies currently responsible for each. The existing system of HHS agency regulation can effectively be applied to the transplant field with little or no major realignment of agency oversight. There may need to be an adjustment of the current regulation of tissue by the FDA.

I would like to thank the Senator for allowing American Red Cross Tissue Services to share our concerns about the future regulation of transplantable tissue. Tissue banking has produced extraordinarily safe tissue on a voluntary basis for decades. Now as the field has grown and matured, we look forward to working with the Congress and the Department of Health and Human Services to develop effective regulation for the safety and effectiveness of this precious resource.

PREPARED STATEMENT OF DR. CHARLES B. CUONO

Senator Kennedy, Senator Simon, Members of the Committee, Ladies and Gentlemen:

My name is Charles Cuono: I am President of the American Association of Tissue Banks. I present the Association's position on the important issues raised by the Human Tissue Transplantation Act.

We believe that any program of oversight or regulation of tissue banks must embody three fundamental principles:

1. Compulsory registration of all tissue banks.

2. Establishment of uniform donor screening criteria based on recommendations from recognized experts in the field.

3. Establishment of a tracking system capable of reconciling each step of transit of all tissues from donor to recipient. Such a system will embody a standard reporting protocol for suspected disease transmission.

Based on our careful analysis, we conclude that S2908 fails to adequately address these three fundamental principles. Furthermore, S2908 relies on a voluntary system, namely, the National Council on Tissue Transplantation. In almost every way, that proposed voluntary Council duplicates the existing voluntary system established more than 10 years ago by the American Association of Tissue Banks. AATB's system of oversight, I should note, is operated at no expense to the taxpayer.

It is our view that an expert Study Group, Panel or Task Force should be convened to address these complex issues. Areas which must be examined include:

- A tightened definition of human tissue. For example, the term "biological transplants" could differentiate biological tissues from "mechanical implants." A human heart valve, though analogous to a mechanical heart valve in terms of its functional activity in the recipient, is clearly very different from the manufactured device. Biological tissue is simply not manufactured to codified written specifications. Lack of such a discriminating definition in the Device regulations may have contributed to FDA's current position on regulation of human heart valves as Class III medical devices.

- Consideration of human tissue as a Biologic and/or monitored under the statutes of both Biologics and Devices within FDA.

- The advisability of an exemption from the usual investigational use requirements for tissues that have been in use for long periods of time and for the banks that provide them.

- Development of specific GMPs (Good Manufacturing Practices regulations) for biologic tissues, reflecting what has already been learned and formulated as the GMPs for Blood and Blood Components.

- Examination of the standards and procedures for tissue banking already developed by AATB.

- Development of a system to track all tissues from donor to recipient and back.

- Development of a system of uniform reporting of suspected or actual incident of disease transmission.

- Development of standard donor screening criteria to be applied to all donors for all human tissue acquisition.

- Examination of the adequacy of training standards for tissue bank personnel.

- Consideration for reclassification of human heart valves to a more appropriate category, perhaps as Class II medical devices. While we are firmly committed to ensuring safety of donated human tissues, we feel our accredited member banks that provide allograft heart valves are experiencing what we believe to be unreasonable mandates for filing applications for IDEs (investigational device exemptions), mandates that, to our knowledge, have not been applied to any other biological material. We have requested FDA on several occasions to reconsider its position--but to date, to no avail.

While our Association promulgates standards and solicits voluntary participation by all tissue banks, we recognize that uniform nationwide compliance with established standards can be guaranteed only through mandated oversight by an external agency. In fact, our Association is currently working with

the American Association of Blood Banks and the College of American Pathologists to develop an effective, economic system to track the disposition of human tissue for transplantation. We feel that federal oversight of this developing program is essential.

AATB is the not-for-profit professional organization, formed in 1976, which currently represents nearly 1000 individual and institutional members engaged in all aspects of tissue banking. Members of AATB formulate standards that govern the acquisition, preparation, distribution and banking of tissues and cells for transplantation. Our guiding philosophy in the development and promulgation of these standards and procedures has been to assure maximum safety to the recipient of the tissue transplants, whether it's a bone graft to avoid amputation, skin to protect burned areas, or a human heart valve to avert a life-threatening condition.

Our commitment to safety is best exemplified by our vigorous program of inspection and accreditation of tissue banking facilities, a program that we feel has had an impact on the impressive record of safety in the field of human tissue transplantation. Of the estimated more than three million transplants completed in nearly a decade since the identification of HIV, tissue from only two donors has been documented to have transmitted the AIDS virus. AATB's voluntary accreditation program was instituted in 1983, and every major tissue bank in this country has voluntarily applied for this accreditation. Of the 400 banks reported by the U.S. Public Health Service, nearly 100 are accredited or have applied for accreditation by AATB; 100 are eye banks, members of the Eye Bank Association of America, which has its own accreditation program; approximately 100 are identifiable semen banks, which are about to be regulated under FDA statutes for Biologics and most of the remaining banks are predominantly small hospital facilities that retrieve and store bone from living donors, for example, for hip replacements. AATB's accreditation process has benefited considerably from the informal review, continuing dialogue and spirit of helpfulness which has been established and maintained with the staffs of both FDA and CDC.

AATB has also developed and implemented educational programs, technical courses and examinations for the purpose of training and certification of the technical personnel working in tissue banks. We examine at least 100 candidates annually and have certified more than 400 tissue bank specialists thus far.

In conclusion, the American Association of Tissue Banks appreciates the opportunity to present our assessment of the Human Tissue Transplantation Act of 1992. Our recommendations are based upon our long-standing commitment to recipient safety and more than 20 years of experience in the development, promulgation and voluntary oversight of standards for the tissue banking community. In addition this analysis and testimony also reflect my perspective on these issues as a transplant surgeon, tissue banker and chief administrator of the leading professional tissue banking association in the United States. AATB stands ready to assist and cooperate with the development of federal policies to ensure the safety of banked human tissue for transplantation nationwide.

Charles D. Cuono, M.D., Ph.D., President
American Association of Tissue Banks
Professor and Director of the Burn Center,
Yale University School of Medicine
Director, Yale Tissue Bank, New Haven, Connecticut

PREPARED STATEMENT OF JEFFREY SANDLER

Mr. Chairman and Members of the Committee, I am Jeffrey Sandler, Executive Director of the Mile High Transplant Bank located in Denver, Colorado, and a member of the Executive Committee of the National Tissue Bank Council ("NTBC"), an organization comprised of 18 of the oldest and largest nonprofit tissue banks that distribute the majority of human musculoskeletal tissue intended for transplantation. I am pleased to appear before you today to discuss the National Tissue Bank Council's views on S. 2908, the "Human Tissue Transplantation Act of 1992." I am accompanied by Steven Gitelis, M.D., an orthopaedic surgeon with a specialty in tumor surgery whose practice includes the transplantation of large tissue grafts at Rush-Presbyterian, St. Luke's Medical Center, and who is the Medical Director of the Regional Organ Bank of Illinois tissue bank.

At the outset, we wish to commend Senator Simon for his leadership in seeking to assure better protection of the public health through uniform regulation of tissue banks and human tissue intended for transplantation.

The NTBC supports Senator Simon's legislation because it believes that uniform national standards for the identification of donors, and the recovery, processing and distribution of tissue will provide needed assurances that human tissue is safe and effective for all transplant recipients. 1/ The NTBC believes that this legislation is of critical importance to the public health. Moreover, the legislation is carefully designed to insure that regulation of human tissue will preserve the altruistic nature of donation which, in turn, will help assure an adequate supply of human tissue for transplantation.

1/ As is the case with most broad-based organizations, not every member of the NTBC agrees with each provision of S. 2908. Some tissue banks have expressed concern over the bill's preemption provision, for example, and others do not support the self-regulating approach that could result from establishment of the National Council on Tissue Transplantation.

If the regulation of human tissue as a medical device subject to investigational device exemptions ("IDEs") and premarket approval ("PMAs") continues, it could possibly lead to a change in the willingness of individuals to donate tissue. Currently, Organ Procurement Organizations and other charitable entities encourage donors to give the gift of life through donation of tissues to nonprofit tissue banks. If regulation of human tissue as a medical device proceeds, however, proprietary entities, able to meet the costs of IDEs and PMAs will likely predominate the tissue banking community. There is little doubt that tissue donation could decline significantly if donors think that their own tissue, or the donated tissue of a loved one, is being commercialized and sold for profit by a proprietary tissue bank.

Summary of NTBC's Position

As presented in greater detail later in my statement, Mr. Chairman, NTBC's position on regulation of human tissue may be summarized as follows:

- Human tissue is not made by man; its supply is wholly dependent upon the willingness of donors and their families to donate tissue to others. Any regulatory scheme applicable to tissue transplantation must not only protect the public health, but must also be crafted to preserve altruism and adhere to the spirit of the National Organ Transplant Act of 1984.

- Any legislation should recognize that, in this field in particular, standards should be developed by, or in close consultation with, the scientific and medical professionals and organizations within the transplantation community. Ultimately, such standards should be required of all tissue banks in this country, either through requiring adherence to professionally developed standards by using the federal reimbursement system, or through direct Food and Drug Administration ("FDA") regulation.

- Congress must develop a means of traceability of human tissue under which all donors and recipients of human tissue may be identified in case of potential transmission of communicable disease.

- Congress should bring to a halt the existing crazy-quilt method of regulation of human tissue -- sometimes as a medical device, sometimes as a drug, sometimes as a biological product, and sometimes not at all -- and replace it with uniform regulation similar to that now in place for blood products.

- Regulation of human tissue should not be through the premarket approval approach, which involves the

treatment of clinical data as proprietary information not available to others, threatens reimbursement for transplantation and is medically unnecessary in the face of 30 years of experience with tissue transplantation. Instead, standards for types or classes of human tissue should be established in order to insure safety and efficacy based on valid and meaningful scientific data.

- Tissue banks themselves should be identified and registered by FDA and subjected to reasonable standards governing testing, processing and distribution of human tissue.

Position on the Use of Professional Standards

At the outset, Mr. Chairman, it is important that NTBC clarify its position on the use of "voluntary," or professional standards to insure the protection of the public health. As you know, under S. 2908, the Secretary of Health and Human Services is required to contract with a nonprofit National Council on Tissue Transplantation (the "Council"), a membership organization of tissue banks and others, which is charged with the development of professional standards for the processing and distribution of human tissue by tissue banks, as well as standards for a type or types of human tissue itself. These standards must be met by all tissue banks who are members of the Council. FDA may promulgate mandatory standards on its own for tissue banks, but need not do so. If FDA determines that professional standards are sufficient to insure patients of reasonable assurance of safety and effectiveness of tissue, it may decline to promulgate its own standards for such tissue.

We recognize that there exist a great variety of opinions throughout the transplant community as to the appropriate use of professional standards. The NTBC would support an approach under which all tissue banks are required to be members of the Council, thus subjecting all tissue banks to professional standards. This could be accomplished, for example, through a requirement that, as a condition of participation in the Medicare program, hospitals may only use tissue from banks who are members of the Council. A system like that proposed in your bill may be sufficient if enforced through a federal reimbursement mechanism.

Mr. Chairman, we point out several potential advantages of use of professionally developed standards:

- They can be developed quickly, since they are not dependent upon the cumbersome notice and comment rulemaking process.
- They can be amended quickly to reflect changes in technology.
- They can be developed and imposed at virtually no expense to the federal government, through imposition of user fees.

Thus, Mr. Chairman, we believe that this Committee strongly consider using the expertise of professionals in the tissue transplantation field and related communities to immediately put in place an enforceable system of regulating the procurement, processing and distribution of human tissue intended for transplantation. We emphasize that, under S. 2908, if at any time such a system is determined to be inadequate, the Secretary may begin the regulatory process.

Background

Transplantation of human tissue is not a new technological breakthrough -- as Dr. Gitelis will present in greater detail, tissue grafts have been collected and transplanted successfully for decades. However, two fairly recent events have focused attention on the need for legislation to regulate the collection, processing and transplantation of human tissue. The first involved transmission, approximately one year ago, of the HIV virus from an organ and tissue donor in Virginia to three tissue transplant recipients and four organ transplant recipients. The second involves recent efforts by FDA to classify human allograft heart valves as Class III medical devices subject to premarket approval requirements. Both of these developments demonstrate the need for a well-reasoned regulatory scheme, like the one proposed in S. 2908, that will standardize and control the quality of human tissue.

Currently, there is little in the way of mandatory regulation of human tissue. No mandatory uniform scheme exists

to assure that donor tissue is properly tested; nor is there a mandatory mechanism to trace transplanted tissue. Moreover, no binding standards for processing human tissue exist. The federal government closely regulates blood banks and blood products, but there are no uniform mandatory standards for tissue banks to prevent the transmission of disease or otherwise assure that human tissue is safe and effective for transplantation. There is also no national requirement for licensure, registration or inspection of tissue banks, despite the fact that there are an estimated 100 - 400 tissue banks nationwide and that more than 300,000 transplants of musculoskeletal allograft tissue are performed in the United States each year. 2/

To date, most of the oversight of tissue and tissue banks has been done through accreditation by voluntary membership organizations such as the American Association of Tissue Banks ("AATB") and through voluntary compliance with professional guidelines and standards published by these organizations. However, not all tissue banks have chosen to be accredited by the AATB. Although the AATB's accreditation process is quite thorough and requires accredited tissue banks to comply with the AATB's published standards, such accreditation is completely voluntary and has not been sought by the vast majority of U.S. tissue banks. Only a little over 40 tissue banks operating throughout the country have been fully accredited by the AATB. This lack of participation in organizations with professional standards underscores the fact

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2/ An accurate assessment of the total number of tissue banks is impossible, since there is no national registration system of such banks. The estimate of 400 banks is derived from a recent report by the Department of Health and Human Services entitled "Tissue and Organ Transplantation Assessment Report." That estimate includes sperm banks and eye banks. However, experience in the State of California, which recently enacted legislation regulating tissue banks, indicates that there may be as many as 300 such banks in California alone. (Communication between James Forsell, Ph.D., Executive Director, Northern California Tissue Bank, San Francisco, and Department of Health Services of California.)

that a purely voluntary process cannot take the place of a sound scheme to control and standardize the quality of transplanted tissue.

Public Health Need for Legislation

While the risk of HIV transmission initially raised the public's awareness of the need for enforceable uniform tissue bank standards, concern about the lack of appropriate regulation has recently been heightened by reports of abuses and controversial practices by some tissue banks. One of our members has experience with a tissue bank having recovered and distributed tissue from a donor known to have tuberculosis. There have also been reports of individuals falsifying donor records; and of donor tissue being imported into the U.S. that is of unknown origin and of questionable quality. There are reports of routine recovery of donors as long as 48-72 hours after death -- notwithstanding AATB guidelines that suggest that no recoveries should be made after 24 hours. Furthermore, because most tissue is not subject to any regulation, there is no control over the representations that tissue banks make about the donor, the tests that have been performed on the tissue to prevent contagion, or the procedures used to process the tissue.

Although the practice of providing tissue for transplantation has been relatively safe, the risk of disease from transmission still exists. Currently, however, the danger of HIV and other disease transmission lies less in the failure of the availability of effective laboratory testing to detect and control HIV and other viruses, and more in the failure of tissue banks to adhere to uniform procurement and processing standards, and of hospitals and surgeons to only use tissue

from banks that adhere to such standards. 3/ In addition, traceability of all transplanted tissue is vital.

. Overview of FDA's Patchwork Regulatory Scheme

At present, FDA regulation of human tissue that does exist is accomplished under a variety of schemes, predicated upon few, if any, rational or guiding principles. The FDA currently regulates certain cell therapies as investigational new drugs and intends to require the approval of a product license application for these cell-therapies as biological products under the Public Health Service Act. Unprocessed bone marrow, however, is excluded from these FDA requirements. Blood is also a material which FDA regulates as a biologic. FDA requires establishments that ship blood products interstate to be licensed as a producer of biologic products, and blood establishments must register and list all products which they produce and comply with regulations setting forth good manufacturing practice requirements for blood products.

In contrast, dura mater, corneal lenticules, umbilical veins, allograft cultured skin and, now, allograft human heart valves are, or are proposed to be, regulated by FDA as medical devices. The type of regulation varies considerably according to the type of tissue regulated. Some tissues, classified as medical devices, are subject only to general controls, such as good manufacturing practice requirements. Others, such as corneal lenticules and human heart valves are required to undergo premarket approval. Notably, however, nothing in this piecemeal scheme provides for the standardization of tissue

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3/ Transplant surgeons and hospitals agree with our organization that uniform regulation of human tissue is needed. Several months ago, David Sutherland, the president of the American Society of Transplant Surgeons, was quoted in the Wall Street Journal, saying "There have to be some regulation for the tissue banks, as with the organ banks." (May 30, 1991.) In addition, just last year one of our members, the Northern California Transplant Bank, conducted a survey of 84 hospitals which asked, among other things, whether the hospitals felt that there is a need for tissue banks to be regulated by the FDA. Of the 84 hospitals surveyed, 71 percent responded in the affirmative.

banking practices nor are tissue banks routinely inspected by FDA to insure that the tissue they are procuring, processing and distributing is safe.

Thus, Mr. Chairman, federal regulation of human tissue is haphazard and largely ineffective. In different Centers of FDA, differently trained personnel apply different rules to human tissue. What is needed is a uniform approach applicable to the entire field of tissue transplantation.

Application to Medical Device Law to Human Heart Valves

On June 26, 1991, the FDA issued a "Notice of Applicability of Final Rule" that "clarifies" a May 1987 rule that all replacement human allograft heart valve processors are required to submit IDEs and PMAs under the medical device provisions of the Federal Food, Drug, and Cosmetic Act. Human heart valves were not specifically mentioned in the May 1987 classification rule and accompanying preamble. Rather, the 1987 rule required PMAs for "replacement heart valves," described in the notice as including "valves constructed of prosthetic materials, biologic valves (e.g., porcine valves), or valves constructed of a combination of prosthetic and biologic materials," consisting "of a housing... and a movable portion that performs the valve function."

When it became clear that FDA intended that human heart valves be covered by the 1987 rule, the six non-profit heart valve processors filed two actions in Federal Court contesting FDA's decision to regulate human allograft heart valves as medical devices. First, they filed a petition for review in the Seventh Circuit Court of Appeals, challenging FDA's Notice of Applicability of Final Rule to human allograft heart valves, because it was a final regulation promulgated in the absence of notice and comment rulemaking, as required by the Administrative Procedure Act. The tissue processors then filed an action in Federal District Court challenging FDA's assertion that human tissue is a medical device, under the 1987 rule, requiring premarket approval.

The Courts have not provided the nonprofit heart valve processors with any relief. The Seventh Circuit held that it lacked jurisdiction to grant the tissue processors relief from FDA's decision to regulate human heart valves as Class III medical devices because the Notice of Applicability of Final Rule was not a final regulation subject to review by the Court of Appeals. 4/ The federal government has filed a motion to dismiss the case in the District Court which will be heard on October 30, 1992. Thus, regulation of human allograft heart valves as medical devices proceeds. Only if Congress intervenes will tissue processors be subject to a more rational, appropriate form of regulation that will not only protect public health, but will also insure reimbursement and preserve altruism in our field.

Problems with Regulating Tissue as a Medical Device

Regulation of human tissue under existing medical device law presents serious and unnecessary difficulties to tissue banks, physicians and patients. First, treating human tissue as a "product" under the medical device law is not only unnecessary to ensure its safety and efficacy, it will have significant negative results for the potential availability of tissue to patients. Already, the regulation of human allograft heart valves as Class III medical devices has severely taxed the ability of the six existing non-profit heart valve processors to continue to process human cardiovascular tissue, and makes it unlikely that additional non-profit banks will be able to meet the expensive and time-consuming requirements involved in preparing IDEs and PMAs for the human tissue that they process. Moreover, the PMA process will take months -- perhaps years -- to complete 5/ and has already cost nonprofit

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4/ Alabama Tissue Center of the University of Alabama, et al. v. Louis W. Sullivan, No. 91-2738, Sept. 16, 1992.

5/ If the PMA for corneal lenticules, which is still pending before FDA, is any example, it will take many years for FDA to approve a PMA for human allograft heart valves.

tissue banks over $1.5 million for data collection and IDE preparation.

The problem of cost to tissue banks of preparing and submitting premarket approval applications is exacerbated by the fact that clinical trial data submitted in support of a PMA are withheld from the public, because these data are regarded as trade secrets by FDA. 6/ The impact of this requirement is that such data typically are not shared with others who must submit their own premarket approval applications to gain approval of their "products" -- in this case, human heart valves that tissue banks distribute. While this treatment of clinical data is appropriate in the commercial marketplace, its ramifications are totally inconsistent with the spirit of the National Organ Transplant Act of 1984, which prohibits the commercialization of human organs and tissue intended for use in human transplantation. 7/ Five tissue banks have submitted a joint IDE for human heart valves, and one proprietary company has done so as well. Assuming ultimate approval of PMAs, does it make sense to require the gathering of new data -- at a cost of millions of dollars -- by another tissue bank that desires to procure and distribute human heart valves?

Moreover, Mr. Chairman, placing human tissues under "investigational" status threatens reimbursement under public and private programs for the costs associated with the tissue itself, as well as for the surgical procedures involved in transplantation. While the Health Care Financing Administration ("HCFA") recently agreed to continue coverage of heart valve transplantation procedures under Medicare, private insurers may not follow suit. If private insurance companies do not pay for human tissue under "experimental" status or for the transplantation procedures necessary to implant the tissue, the affordability of tissue transplantation will be severely

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6/ 21 C.F.R. § 814.9 (1992).

7/ National Organ Transplant Act, Pub. L. No. 98-507, 42 U.S.C. §§ 273-741 (1984).

compromised and its availability threatened. Notably, it is also clear that tissue banks will have to increase the costs of the human tissue they process and distribute to offset the costs associated with filing IDEs and PMAs. The PMA requirement has directly resulted in a 50 to 100 percent increase in the cost of processing heart valves -- which has been passed on to patients with little apparent benefit to them.

For these reasons, Mr. Chairman, regulation of human tissue should be by a single regulatory mechanism developed by Congress. There is no reason, in the NTBC's view, that some human tissue should undergo clinical trials under a mechanism designed for drugs and sophisticated medical devices. This approach is nonsensical in the context of human tissue, will cost millions of dollars, take years to complete, and will result in tissue banks receiving a private license to process tissue. What is needed is legislation, such as that proposed by Senator Simon, making transplanted tissue subject to standards based on scientific evidence applicable to all tissue. Under the uniform standards approach of Senator Simon's bill, more tissue will become subject to scientific scrutiny in the next few years than under the current approach, which would require decades to implement, with no benefit to human health.

Comments on S. 2908

Under the proposed legislation, the entire field of tissue procurement, processing and distribution would fall under a standardized approach which does not involve regulation of one tissue at a time. In particular:

- Under either the National Council on Tissue Transplantation or FDA approach, S. 2908 requires the establishment of standards for types or classes of human tissue for clinical use. Under S. 2908, the type of data which may be required to support standards can vary according to the characteristics of the tissue and other factors. Under the proposed legislation, standards may be based in part upon

well-controlled investigations, partially controlled studies, well-documented case history reports or clinical experience in humans, as well as other data which are scientifically adequate to support such standards (including, of course, data that has been collected over the last 30 years). In addition, the standards will be based on the development of data that can be shared by all tissue banks. For reasons set forth earlier, we firmly believe that this approach is in the best interests of physicians and tissue banks, as well as the public health.

- S. 2908 provides for the classification and regulation of human tissue as biological products, consistent with FDA's regulation of other human biological products including blood products and vaccines. This too makes eminent sense because the Center for Biologics Evaluation and Research ("CBER"), which regulates other human biological products, clearly has the expertise to evaluate and, if necessary, develop, uniform national standards for human tissue, and ensure the tissue banking community's compliance with those standards.

- S. 2908 provides a mechanism, whereby for the first time tissue banks will be required to comply with regulations that, among other things, assure that tissue is processed and distributed in accordance with good tissue banking practices designed to provide reasonable assurance that donors are properly screened, and the tissue is properly processed. Again we applaud this portion of the proposal as representing long overdue protection of the public.

- S. 2908 would require uniform recordkeeping of transplanted tissues under federal law, so that the donor and recipient of tissue can be recorded for easy tracing and study. Under the bill, all hospitals participating in the Medicare or Medicaid programs must establish and maintain records relating to the transplantation of human tissue in their facilities in a manner that facilitates the identification of patients who have received the transplanted

human tissue, donors of such tissue and the distributor of such tissue. We endorse wholeheartedly this fundamental effort to insure that potential transmission of disease from infected donors be minimized.

- S. 2908 involves significant reliance on the expertise of experts in the organ and tissue procurement and transplantation community, rather than to burden the FDA with the sole responsibility for developing public standards for human tissue. We recommend serious consideration of substantial use of the scientific and medical professions -- and the tissue banking community itself -- to develop and apply meaningful standards to human tissue for the benefit of the public.

For the foregoing reasons, the NTBC endorses S. 2908 and looks forward to working with Senator Simon, the rest of the tissue bank community, the blood banks, transplant surgeons, Organ Procurement Organizations, hospitals and others in pursuing enactment of reasonable legislation. Action by Congress will be an important step toward better protecting the public health by regulating and controlling the quality of human tissue for transplantation while assuring the altruism necessary to continue availability of life-saving tissue to needy patients.

PREPARED STATEMENT OF RICHARD A. HOPKINS, M.D.

Senator Simon and members of the Committee, my name is Richard Hopkins. I am Director of Pediatric Cardiac Surgery at Georgetown University Hospital and hold various administrative positions with the American Association of Tissue Banks ("AATB"), LifeNet Transplant Services, and actively pursue basic medical research related to human heart valves. However, I speak to you today as a clinical cardiac surgeon who specializes in reconstructive cardiac surgery. While I treat many adults in my practice, I treat an even larger number of children. Thus, I would like to specifically address the effect of tissue regulation on pediatric cardiac surgery.

For some time now, I have been working with the FDA and other agencies on issues involving the appropriate regulation of human tissue. Despite my efforts, and the efforts of other cardiac surgeons, FDA has nevertheless chosen to require premarket approval of human heart valves . . . an undertaking that will have serious adverse consequences for patients, especially children, in need of heart valves.

In my opinion, federal regulatory policy should attempt to preserve altruism in tissue donation, protect patients from unsafe tissue processing and stimulate advances in tissue processing. FDA's approach to regulating human allograft heart valves, instead, threatens to change the altruistic character of the tissue banking community, diminish donors' willingness to donate human heart allografts for transplantation, and stymie advances in tissue processing, with no benefits to human health. FDA's approach is onerous and burdensome. Moreover, it unnecessarily requires tissue banks to reinvent the wheel because it does not rely on much currently available data. 1/ Furthermore, FDA's current approach will not protect the public health soon enough because it will take decades to implement.

Allograft valves were made and designed by God. From an engineering standpoint, they are the most perfect implant we have. Because the valves are natural, there is optimal hydraulic flow and hemodynamics, even where size constraints are imposed either by the size of the patient or by the nature of the cardiac reconstruction. 2/

Moreover, since each prototype already has functioned properly in the donor, there is superior hemodynamic

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1/ The fresh allograft has been used since 1962 (in the aortic position) and 1967 (in the right ventricular outflow tract position) in children, with results that have been excellent and clearly are far superior in specific patient sub-groups. Cryopreserved valves have been used since the mid-1970s worldwide with results that appear superior to fresh transplants. Small implants have improved surgical survival when allografts are used instead of rigid manufactured appliances.

2/ See generally Cardiac Reconstructions at Chapter 2, pp. 16-18.

performance. 3/ Recipients of human allograft valves do not require anticoagulation therapy, since the incidence of thrombo-embolism and hemolysis is extremely low. 4/ This is especially important since children do not respond well to coumadin, the anticoagulant drug that is prescribed for mechanical valve recipients. Such anticoagulants also are contraindicated for women of child-bearing years.

Furthermore, calcification of the human heart valve leaflets is rare, and if it does occur in human valves, calcification tends to be gradual and non-obstructive. 5/ In contrast, it is widely accepted that porcine valves often experience an "extremely accelerated and malignant degree of calcification when implanted in young children." 6/ In fact, it is generally acknowledged that human allograft heart valves are the only acceptable alternative for valve replacement in children, due to the problems of anticoagulation with mechanical valves and accelerated degeneration of porcine valves. 7/

In addition, implantation of human heart valves is relatively easy. Infections following implantation of human valves occur less frequently than with other substitutes, 8/ and the human valve has much greater resistance to endocarditis than mechanical or porcine valves. 9/ Catastropic failures that can occur with mechanical valves are almost non-existent with

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3/ Id.

4/ Id.

5/ Cardiac Reconstructions at 19 (human allografts are "considered competitive or superior to the porcine graft in young patients and those with contraindications to anticoagulation"); see also Clinical Surgery 175-82.

6/ Letter from Dr. Richard Jonas, Associate Professor of Surgery, Harvard Medical School, to Food and Drug Administration, dated November 27, 1990.

7/ See, e.g., Cardiac Reconstructions at p. 19.

8/ Id. at 9.

9/ Id.

human valves. 10/ Most important, the expected life of the human replacement valve is substantially longer than that of the porcine or mechanical substitutes. 11/ They resist wear for a long time and reconstructions can be achieved that allow the child to "grow into" his adult size replacement. By contrast, children who receive a porcine valve usually need to have the valve replaced every 2-4 years due to calcific degeneration. With each operation there is an average five percent mortality.

In sum, the general medical consensus is that human allograft heart valves are substantially superior to other substitutes for most pediatric patients in reconstructing the outflow tract of the right ventricle, for women of child-bearing years, for infected aortic roots and for various complicated reconstructions. Specific patient subgroups, such as neonates, children, women of child bearing age, patients who cannot take anticoagulents and patients with subacute bacterial endocarditis, must have access to human heart valves. While there are often indications for porcine or mechanical heart valves in patients, cardiac surgeons certainly should not be limited by the FDA to the use of only porcine or mechanical valves.

While human allograft heart valves are the best valves we have, they are not perfect. At times, they deteriorate and a few of my patients have experienced some calcification of implanted valves. Accordingly, I am certain that most cardiovascular surgeons support a regulatory mechanism designed to learn more about the nature of tissue processing and assure that processing is of the highest quality. However, classification of human heart valves as "experimental" medical devices, while perhaps appearing to be a simple regulatory approach, does not make any sense in light of the fact that the

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10/ See e.g., Cardiac Reconstructions at 17.

11/ Clinical Surgery at 176; Cardiac Reconstructions at 19.

safety and effectiveness of these human replacement valves has been well documented over the past 20 years and has never been seriously challenged. Porcine heart valves that are explanted from another species, or mechanized valves constructed of synthetic materials quite understandably are regulated as medical devices. But it is not necessary or appropriate to regulate that which man did not make in the same way.

For the foregoing reasons, I would urge you to pursue the regulatory approach that is taken by S. 2908, which makes all transplanted tissue subject to standards based on meaningful scientific evidence. In the meantime, regulation of implantable human tissue as a medical device should be stopped. If it is not, and shortages of allograft valves result, children will suffer real pain, be subjected to multiple surgeries, leading to greater numbers of complications and deaths.

Prepared Statement of Steven G. Anderson

Good morning, Mr. Chairman. My name is Steven G. Anderson, and I am the President and cofounder of CryoLife, Inc. of Marietta, Georgia. I am pleased to have the opportunity to share some of our views on tissue and organ regulation. Like you, we believe that this subject has important policy consequences, and deserves careful thought and public debate.

Let me begin with some background on CryoLife. Founded in 1984, CryoLife, Inc. processes and preserves human cells and tissues for transplant. CryoLife does not procure tissue nor does it own tissue; it provides services to 139 organ and tissue banks throughout North America and Europe.

CryoLife's specialty is ultra-cold preservation of human heart valves. Since 1984, over 900 physicians at 350 medical centers in the United States have implanted more

than 12,000 CryoLife valves.[1] The majority have been used to treat children with congenital heart defects. We are very proud of CryoLife's valves, which have an outstanding record of safety and durability; our audited data show that, 5 years after implant, 89% of CryoLife aortic allograft valves remain functional. Even so, we know that a great deal remains to be learned. Tissue preservation is a science still in its infancy. For example, right now, we are testing a solution called VIP that kills yeasts, bacteria, fungi, and perhaps viruses, including the AIDS virus, on contact - without harming tissue. If our testing works out as we hope, VIP will make better, safer valves, bone, and other tissue.

We also preserve other tissues for transplant, including human veins, bone, and connective tissue. Our vein, for example, is used in coronary bypass when the patient's own vein is not available, and in vascular reconstruction, which can save limbs that might otherwise be amputated. Since 1987, 4,000 CryoLife veins have been transplanted.

Funded by the National Institutes of Health, the U.S. Navy, and CryoLife's own investment, we continue to work on both better methods of preservation and on new applications of existing technology. Together with Colorado State University, we are developing a technology to allow transplantation of human cells onto animal matrices. For example, human cells could be grown on a porcine heart valve, which would then be transplanted into a person, perhaps even the one who donated the cells originally. If it works, the "SynerGraft," as we call it, would solve the supply problem inherent in using human tissue, while eliminating the calcification that make porcine valves undesirable for children.

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1. This is the largest series of human heart valve transplants in the world.

Another of our projects involves the development of a blood-based bio-adhesive that will promote wound healing. Right now, post-surgical bleeding is a major problem, particularly after cardiac surgery. This "human glue" would use the blood's natural clotting mechanism to help stop that kind of bleeding.

Although that background barely scratches the surface of CryoLife's work, I want to turn to some of the regulatory issues before this Committee. Let me start by saying that there is no question in my mind that organ and tissue transplantation should be regulated. The public needs to know that transplanted tissue meets appropriate health and safety standards.

Discussion of tissue regulation is often coupled with discussion of infectious disease transmission. The Public Health Service Task Force on Organ and Tissue Transplantation found that the risk of tissue-related disease transmission is relatively small. Still, it has happened in the past, and we must take all reasonable steps to make sure that it does not happen again. That means regulating both the tissue processor, who is responsible for some of the steps that prevent disease transmission, and the tissue procurement agencies. Procurement agencies are really the front-line defense against disease transmission, because they take the donor histories that screen out high-risk donors and, in some cases, do the serological testing as well.

Regulation can also ensure that only safe and efficacious tissue is transplanted. Tissue in its natural state is perfectly designed for its natural function. But transplantable tissue may well have been dissected, transported in an artificial solution, bathed in antibiotics, irradiated, frozen, stored, thawed, packaged, and transported again. There is a lot of room for error if the process is not carefully designed and executed.

A third reason for regulation is that it imposes a valuable discipline on even the most careful provider. There is no question that preparing the heart valve IDE has improved CryoLife's processing; just writing things down in such detail has caused us to re-evaluate and improve some of our procedures. And bringing our processing into compliance with Good Manufacturing Practices has improved the uniformity and quality of the tissue we preserve as well as our recordkeeping.

I think that, collectively, we have really gone beyond the question of whether regulation has value. The issues now are:

- who should oversee the regulatory system;
- what kind of regulation will get the job done most affectively; and
- what is an appropriate time frame for putting a system in place.

S. 2908 provides one possible set of answers to those quastions. Whila I cannot agree with everything in that bill, it raises the right questions and is a valuable starting point. Our experience with heart valve regulation should also inform our thinking. While the process was initially difficult and uncertain, FDA and the regulated community hava laarned from the experience, and I beliave we are now on tha road to tha right result.

As to tha first question, who should oversee the regulatory system, I firmly believe that the FDA is the only appropriate choice. The issues are important health and safety questions; they daserve FDA attention. And they are going to become important to more peopla as tissue tachnology improves and new applications are invented. FDA has both the experiance and credibility, as well as a nationwide presence to enforce its regulation.

I don't believe that a system that gives primary regulatory authority to the tissue banks themselves can be effective. The AATB has done a good job in developing

standards and a certification program; but this industry is too large and too diverse to come together under a voluntary scheme. And self-regulation is unlikely to be as rigorous as government regulation.

Let me turn to my second question, "What kind of regulation is appropriate?" In entrusting FDA with the responsibility for regulating drugs, devices, and biologics, Congress has provided it with a full range of regulatory tools. In the medical device area, for example, FDA can use premarket approval or set standards to ensure safety and efficacy, or rely on a combination of both. It can require tracking and postmarket surveillance; and it has a wide range of enforcement authority from ordering recalls to banning products entirely.

I believe that we should have their full range of regulatory tools available in regulating human tissue. Standards may be enough to protect the public in some cases. But in other cases, it may be that a standard both sufficiently protective and sufficiently flexible cannot be written. In those cases, other kinds of regulatory tools may be needed.

Whatever regulatory scheme is chosen, it must provide a quick way to review and sign off on changes in the way things are done. Tissue engineering is a science that is moving rapidly. Five years from now, our processes will look very different from today. We cannot afford a regulatory process that stifles innovation and creativity.

Finally, what is an appropriate time frame for putting a system in place? There are over 300,000 transplants of human tissue in the U.S. each year. There are more tissue transplants per year than there are heart pacemaker implants. The time to regulate this industry is now.

One thing that FDA could and should do very quickly is to write regulations for preventing transmission of infectious diseases. This is an area where one set of

regulations could cover all tissues. Minimally, those should mandate:

- the most advanced donor screening and serological testing method;
- a consistent tracking and recordkeeping system that ensures that tissue can be traced from donor to recipient.

Whatever system we choose, we should not paralyze FDA while it is being implemented. In a crisis, someone must have the legal authority to remove a dangerous product from the market. I urge you to write any legislation with that principle in mind.

All of the things I have described above are things that FDA already has the statutory authority to do. And I believe - heart valves notwithstanding - that FDA has the authority to do them in a way that does not disrupt the tissue community or jeopardize the availability of lifesaving tissues. Last October, I testified before the Public Health Service Task Force on Organ and Tissue Transplantation and described how our objectives might be accomplished; I have submitted my previous testimony for the record. If we are looking for precedent, blood and blood products are probably a good analogy. As some of my colleagues here this morning can attest, these have been regulated successfully by FDA for a number of years.

That is not to say that the current way is the only way, and I do not reject legislation out of hand. For one thing, I recognize the very real resource limitations that FDA faces, a problem that may require Congressional action. Isn't it less costly to provide FDA with the funds necessary to regulate tissue than to legislate a new and completely separate regulatory entity? It is worth remembering that FDA's regulatory system has stood the test of time.

Thank you.

TESTIMONY OF
STEVEN G. ANDERSON
PRESIDENT, CRYOLIFE, INC.

Before the
Public Health Service Hearing on
Federal Regulation of Organ and Tissue Transplantation

October 16, 1991

Good morning Mr. Chairman and members of the panel. My name is Steven G. Anderson and I am the President and cofounder of CryoLife, Inc., of Marietta, Georgia. I'm pleased to have the opportunity to share some of our thoughts on tissue and organ regulation. Let me begin with some background on CryoLife.

Founded in 1984, CryoLife, Inc. was the first company in the United States to specialize in the ultra-low temperature preservation of human cells and tissues for transplant. CryoLife does not procure tissue; it provides preservation services to 250 organ and tissue banks throughout North America, Canada, and Europe. Cryolife's specialty is preserving human heart valves. There are now 650 physicians at 350 medical centers in the U.S. implanting CryoLife-preserved valves. Since 1984, approximately 10,500 valves have been successfully implanted, and we believe that 75 to 80% of all human heart valves preserved in the United States are preserved by our laboratory.

We also preserve other tissues for transplant, including human veins, bone, and orthopedic connective tissue. We are particularly proud of our vein transplants for peripheral vascular reconstruction, which can eliminate the need to amputate limbs of people with severely compromised vascular systems, and our menisci (knee tissue), which can be transplanted into severely damaged knees to alleviate debilitating arthritic conditions. In 1991, CryoLife will process tissue from over 3,400 separate donors.

CryoLife also has an extensive research and development commitment. Since 1987, the company has received seven research grants from the National Institutes of Health and the U.S. Navy for projects involving the preservation of human cells and organs. In addition to its grants, the company spends about 12%

of its revenues on research and development. Our most exciting research involves a tissue and organ decontamination solution and perfusate that our preliminary research shows kills yeasts, bacteria, fungi, and perhaps virus on contact. We hope that this solution will be effective on whole organs and transplantable tissue. We are also testing a new blood cryopreservation method that eliminates the need for a costly washing step prior to transfusion.

When CryoLife opened its doors in 1984, there were few standardized procedures for ensuring tissue safety. Over the years, we evolved our own system, based on the quality assurance systems commonly found and practiced in the implantable device industry. Our system continually improves as constant technological advances are translated into safer screening and preservation methods.

Our communicable disease screening system has four key elements.

- The first is donor history and screening. Although CryoLife does not procure tissue, it accepts tissue only from organizations that use the CryoLife procurement protocol or an equivalent. Included in the protocol is a donor screening procedure, designed to elicit relevant information about the donor, including risk factors, that would put the donor at risk for HIV.

- The second step is serological screening; we screen for multiple viruses, including HIV and hepatitis. Because so much thought has been devoted to developing regulations to ensure the safety of the nation's blood supply, we have adapted these regulations to our tissue, and use all tests that are FDA-mandated and licensed for blood. In some cases, we start using new tests before FDA requires them, such as HIV 2, and, for some tests, we hold ourselves to tighter standards than FDA requires. With limited exceptions, we do our own viral screening even if the procurement organization has already done so, because we want to ensure that we have timely and complete results.

- Our third step is a microbiological treatment that kills bacteria and fungi, followed by testing to ensure that the treatment has done its job. We discard tissue that doesn't meet our release standards in any of these three areas.
- Finally, we keep complete procurement and processing records as well as physician and patient records so that we can track tissue from its source to the recipient and back again.

Our system is very similar to the patient implant information report that has been standard practice for many implantable devices. We are currently improving the system we use to locate patients who are no longer in contact with the implanting physician.

With that background, let me comment on some of the questions that you have posed for this hearing. First, I would like to congratulate you on the work of your task force. We agree with your conclusion that the risk of transmitting AIDS through transplantation is very small. We also agree that there are steps that might be taken to minimize not just the AIDS risk, but other risks as well.

Your threshold question is whether federal organ and tissue regulation is needed. No matter what product approval process is used, CryoLife believes that the federal government should have the key government role in ensuring the safety of the nation's transplantable organs and tissues. As you have heard, we have spent years developing and refining our safety program. In continuing to do so, we monitor carefully the government's guidance, and adapt it to our own situation. We believe that the government should adopt mandatory requirements at least in the areas of donor screening, aseptic processing, and recordkeeping. We further believe that the government should have a strong enforcement role, which would include facility registration and inspection.

The federal government is the only organization that can handle the job. There is no strong, independent, and credible organization to make voluntary standards work. There is

not even a single organization to which every affected organization belongs or could belong, let alone one that could handle standard-setting and enforcement in this important field.

Only the federal government can establish the level playing field that is needed, where for-profit and non-profit organizations must meet the same standards of safety and effectiveness, where each kind of organization is required to carry out the safety functions that it can handle most effectively, and where organizations in one state must meet the same requirements as those in another. There are now more than 300,000 tissue transplants a year in the U.S., almost all of which have an interstate component. State-by-state regulation will exacerbate the scarcity problem, drive up costs, curtail competition, and discourage innovation. Transplantation is a national effort and it should be regulated accordingly.

In advocating federal regulation, however, I want to stress that the best approach is one tailored to the particular needs of organ and tissue transplantation. These activities are unusual in several respects, and regulating them may require some unusual steps. The first, of course, is the matter of supply. Tissue scarcity is still the number one public health issue. People still die because suitable tissue is not available. Protecting the public health requires a government presence in alleviating scarcity as well as in ensuring safety. At a minimum, the government should ensure that it does not, in the name of other goals, erect unnecessary barriers to procurement and utilization.

The second special feature is the fact that this activity is well-established; patients and health professionals rely on transplantable tissue. All of us in this field are going through a challenging transition period with heart valve regulation. I hope that the government can achieve its ends without disrupting the important health benefits already being achieved through transplantation.

A third consideration for the federal government is a recognition of the work that lies ahead. Preservation

technologies are developing rapidly, and we should take care not to create an approval process that will impede the development or implementation of new technology. For example, we all know that the best screening in the world may not detect HIV in a donor during the window period. That is in part why we are so excited about the prospect of a treatment that will kill virus. At best, the government should increase its commitment to developing solutions to problems like these; at a minimum, it should not create barriers to implementing solutions developed by others.

Within those broad parameters, I would like to comment on two specific regulatory issues. The first is the question of who should be regulated. FDA has already regulated processors of several tissues, has stated its intention to regulate heart valves processors, and has put us on notice that we should expect regulation of processors of other tissues in the future. That is a good place to start, but it is not the place to stop.

We would like to see a similar focus on procurement agencies. This does not mean a UNOS-like organization for tissues. UNOS may make sense for solid organs, but a federally-managed system is not needed, nor would it work, for tissues. Tissue procurement is too decentralized and it need not operate by monopoly.

We would, however, like to see the government set safety-related procurement standards. After seven years of working with 250 procurement organizations, we have learned that there is a variety of expertise within these groups. A processor like CryoLife can establish its own standards and encourage procurement agencies to meet them, but it cannot police them. Further, the current system, in which procurement organizations and processors sometimes duplicate each other's work, is inefficient and costly. Far better to have the government adopt a uniform set of standards for all tissue procurement organizations and enforce those standards. I understand that FDA could, under the communicable disease authority of the Public Health Service Act, establish such a regulatory system, and I urge that it do so as soon as possible. To assist it, FDA might

consider a task force composed of members broadly representative of the organ and tissue community, as well as public representatives.

Second, you asked for comment about the desirability of establishing a reporting chain to provide early warning of contaminated tissue. I have already described CryoLife's tracking system. Every participant in transplantation should have a similar system. An effective tracking system would eliminate any need for a costly patient registry.

As a matter of theory, no one would dispute that contaminated tissue should be recalled, that there are instances in which look back is appropriate, and that the tracking system should be used for those purposes. Designing such a system, however, poses some practical problems. Most difficult is designing criteria for determining when a patient event should trigger reporting, when a report should trigger a recall, and who should decide when the criteria have been met. For example, we do not want to create a situation in which a false positive AIDS test could trigger a scare, or one in which a transplanted tissue is blamed for AIDS developed by an IV drug abusing transplant recipient. Designing a workable system requires careful thought, and we suggest that it too should be considered by the task force.

CryoLife believes that, working together, this community can make transplantation even safer. We are committed to that goal.

Thank you.

October 31, 1991

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Human Organ and Tissue Transplantation
Docket No. 91N-0318

Dear Sir:

Enclosed are four copies of a comment submitted by CryoLife, Inc. to supplement the testimony of Steven G. Anderson, President of CryoLife, Inc. at the October 16, 1991 hearing on Human Organ and Tissue Transplantation.

Sincerely,

Kate C. Beardsley

Enclosures

October 31, 1991

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 1-23
12420 Parklawn Drive
Rockville, Maryland 20857

Re: Human Organ and Tissue Transplantation
Docket No. 91N-0318

During the October 16, 1991 Public Health Service Hearing on the Federal Regulation of Organ and Tissue Transplantation, many witnesses testified to the need for enforceable standards designed to reduce the risk that transplanted tissue may spread AIDS or other communicable diseases. Several questions were raised, however, about whether FDA has sufficient authority to regulate in this area. CryoLife believes both that standards are needed and that FDA has ample authority under Section 361 of the Public Health Service Act to impose them.

CryoLife, Inc., of Marietta, Georgia, preserves human cells and tissues for transplant. The company is the

nation's largest processor of human heart valves; since 1984, approximately 10,500 CryoLife-preserved valves have been successfully implanted. CryoLife also preserves human veins, bone, and orthopedic corrective tissue for transplant and has an extensive research and development commitment.

As stated by Steven G. Anderson, CryoLife's President, at the October 16 Public Health Service hearing,[1] CryoLife believes that the federal government has an important role in ensuring tissue safety. To minimize the risk that disease might be spread through transplanted tissue, the government should adopt regulations that require donor screening, serological testing of donors, and appropriate treatment of tissues. These regulations should specify which of the institutions that handle tissue is responsible for each function so that duplication can be eliminated and accountability is clear. The institution required to carry out each function should keep careful records both of the testing and treatment it has undertaken and of the source and destination of the tissue. The government should monitor compliance with the regulations through facility registration and inspection.

These regulations can be issued pursuant to Section 361 of the Public Health Service Act ("Section 361"), which grants the Surgeon General authority to

> make and enforce such regulations as in his judgment are necessary to prevent the introduction, transmission, or spread of communicable diseases . . .[2]

This authority has been delegated to the Commissioner of the Food and Drug Administration ("FDA") with respect to items

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1. A copy of Mr. Anderson's October 16 testimony is attached hereto.

2. 42 U.S.C. § 264(a).

regulated by FDA.[3] To carry out and enforce the regulations, FDA

> may provide for such inspection, . . . disinfection, sanitation, . . . destruction of . . . articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in [its] judgment may be necessary.[4]

The statutory authority is extremely broad, limited only by FDA's "judgment" as to what is "necessary." One court explained the reach of Section 361 as follows:

> Congress has granted broad, flexible powers to federal health authorities who must use their judgment in attempting to protect the public against the spread of communicable disease.[5]

It seems quite clear that any human tissue that could transmit communicable disease to a recipient would be an authorized object of regulation under the statute.[6] The statute imposes no limits on who or what may be regulated; thus, if necessary, FDA may regulate the tissue itself, the institutions that handle it, or both. The statute may even be used to regulate intrastate tissue transfers as long as

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3. Enacted in 1944, Section 361 originally granted this authority to the Surgeon General. Under the 1966 administrative Reorganization Plan No. 3, 31 Fed. Reg. 8855 (June 25, 1966), the authority was transferred to the Secretary of Health, Education, and Welfare (now Health and Human Services). The Secretary, in turn, delegated the authority to FDA, under 21 C.F.R. § 5.10(a) (4), in relation to: "biologicals (including blood and blood products) . . . food . . . drugs, devices, . . . and other items or products regulated by [FDA]." "Other items or products" that FDA regulates under this authority include: turtles, psittacine birds, and lather brushes. 21 C.F.R. Part 1240.

4. 42 U.S.C. § 264(a).

5. Louisiana v. Mathews, 427 F. Supp. 174, 176 (E.D. La. 1977).

6. In the past, FDA has issued regulations covering such disparate products as shellfish, milk, pet turtles and birds, lather brushes, and garbage to be fed to swine. 21 CFR Part 1240. FDA also cites section 361 as an authority source for regulations governing its enforcement and administrative policies, 21 C.F.R. Parts 7 and 10, as well as for those governing: biologics, 21 C.F.R. Parts 600-680; good manufacturing practices for human food production, 21 C.F.R. Part 110; low-acid foods for humans, 21 C.F.R. Part 113, and animals, 21 C.F.R. Part 507, bottled drinking water, 21 C.F.R. Part 129; and drug labeling, 21 C.F.R. Part 201. FDA regulations suggest it will exercise its authority only in the event of inadequate local control. 21 CFR § 1240.30.

such regulation is reasonable to prevent the interstate spread of disease.[7]

The statute is equally broad with respect to the means of regulation, permitting any "measures" that are "necessary." Even bans of particular products likely to spread diseases are permissible as long as they meet the necessity standard.[8] None of the measures needed to regulate human tissue are as intrusive as a ban would be.

Several of the measures that CryoLife recommends have been instituted before under Section 361. For example, prior to the ban on small turtles, FDA required testing of such turtles,[9] much as it would require donor screening and testing under CryoLife's proposal. The fact that, unlike small turtles, testing of human tissue would be performed on donor serum and through questionnaires rather than on the tissue itself, should make no difference in determining whether testing is authorized by the statute. FDA has also required and set standards for treatment of articles to kill contaminants,[10] a direct analogy to the CryoLife proposal. Finally, the agency has defined its inspection authority in several Section 361 regulations.[11] While CryoLife has

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7. Louisiana v. Mathews, supra, at 176.

8. Id.; 21 CFR § 1240.62, Turtles intrastate and interstate requirements.

9. 37 F.R. 24,670 (November 18, 1972). The regulations required importers of small turtles or viable turtle eggs to have such turtles sold in interstate commerce certified. To receive certification, each shipment of turtles was subject to testing procedures specified in the regulations and performed by a "laboratory licenses in microbiology pursuant to section 353 of the Public Health Service Act.

10. See 21 CFR § 1240.61, "Mandatory pasteurization for all milk and milk products in final package form intended for direct human consumption" and 21 CFR § 1240.70, "Lather brushes," for examples of FDA required treatments.

11. See 21 CFR § 1240.70, Lather brushes, and 21 CFR 1250, Interstate conveyance sanitation, for statements of FDA inspection authority under Section 361.

identified no examples in which FDA has required facility registration under Section 361,[12] registration is in effect an adjunct to inspection. Developing an effective inspection program requires that FDA have knowledge of where the tissue and the facilities that handle it are located. Consequently, registration seems justifiable as a measure necessary to prevent the spread of disease.

Although CryoLife is also unaware of any situation in which FDA has required recordkeeping under Section 361, such requirements seem equally within the authority provided by Section 361. A capacity to track the movement of particular tissue is essential to preventing the spread of disease. Should it be learned that a particular donor's organ or tissue has transmitted disease, preventing further disease transmission may require that tissue be recalled, which can be accomplished most effectively if the tissue can be tracked. Testing records and donor screening information may also be helpful in determining whether a tissue suspected of disease transmission was actually involved. In addition, FDA should have access to records to help determine compliance with the regulatory requirements.

In sum, CryoLife believes that FDA has both the authority and the responsibility to establish standards designed to prevent the spread of communicable disease through human tissue transplantation. FDA's mandate under Section 361 to protect the public from the spread of communicable diseases underscores the agency's responsibility to do so.

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12. FDA has, however, required persons handling certain products to obtain permits. If FDA can require permitting, it seems reasonable that it could require registration because, like registration, permitting, at least in part, achieves the purpose of facility identification.

Association of Biotechnology Companies

September 1, 1992

The Honorable Paul Simon
U.S. Senate
Washington, DC 20510

Dear Senator Simon:

The Council of Tissue Technology (CTT) of the Association of Biotechnology Companies has reviewed S. 2908: "The Human Tissue Transplantation Act of 1992."

The Council supports federal involvement in tissue banking, but the CTT has some reservations about S. 2908 and believes that the bill needs to consider some additional issues before we can accept it. Although voluntary standards promulgated by the bill are desirable, the CTT is concerned about compliance to such standards and whether the lack of compliance would trigger a subsequent harsher reaction by Congress. And there is a need to pre-empt state legislation regarding tissue bank operations, a need beyond the abilities of voluntary standards.

We would prefer a public health solution authorizing the direct regulation of tissue services by the Food and Drug Administration (FDA). Such legislation would:

1. Impose requirements for establishment (facility) licensing, donor screening, and tissue traceability.

2. Utilize the principles of Good Manufacturing Practices (c GMPs) for Biologics as contained in 21 CFR 600.

3. Pre-empt state legislation regarding tissue bank operations.

In conclusion, we believe that strong, enforceable regulations of tissue services is in the national interest. ABC would be happy to meet with you and your staff as well as with other groups supporting the bill to resolve these concerns. Although ABC keeps an open mind regarding S. 2908, we will have to vigorously oppose the bill unless these concerns can be resolved.

Yours very truly,

William E. Small
Executive Director

EYE BANK ASSOCIATION of AMERICA

Dedicated to the Restoration of Sight since 1961

October 22, 1992

The Honorable Paul Simon
U.S. Senate
462 Dirksen Senate Office Building
Washington, D.C. 20510

Re: THE HUMAN TISSUE TRANSPLANTATION ACT OF 1992
(S. 2908)

Dear Senator Simon:

The Eye Bank Association of America (EBAA) appreciates the opportunity to comment on S. 2908, The Human Tissue Transplantation Act of 1992. We support the appropriateness of standards in the areas of procurement, processing and distribution which S. 2908 proposes. Indeed, the EBAA took the lead almost a decade ago in developing standards which govern these areas and others of tissue banking services, specifically relating to the eye.

Further, the eye community reinforced its commitment to public accountability and patient safety in its pursuit of regulation under the Clinical Laboratories Improvement Act Amendments of 1988 (CLIA). Inclusion under this Act has enabled the EBAA to enforce consistent improvements in procedures for tissue procurement and processing, in record keeping and in other key areas vital to public health.

We offer the following observations and recommendations for consideration.

1. Background:
The EBAA is a non-profit organization of 98 member eye banks that represents over 90% of the eye banks in the United States. Our members have pledged their mission as "dedicated to the restoration of sight".

Through the procurement and distribution of corneal tissue and eyes for transplantation, education, and research, our members - in over 150 locations - contributed to the success of 43,000 corneal transplants in 1991; moreover, as a result of our history of voluntary compliance to strict medical standards and rigorous quality control, there have been more than 420,000 documented corneal transplants handled by U.S. eye banks in the last two decades, with a remarkable history of safety.

Since our inception in 1961, founded by the Committee on Eye Banks of the American Academy of Ophthalmology, our organization has consistently reviewed and refined our medical standards and procedures to a level of success unparalleled in

the greater transplantation arena. Over 90% of the operating eye banks in the U.S.- all EBAA members - voluntarily comply with EBAA peer review and certification.

As the cornerstone of our organizational services, our medical standards ensure quality control, patient safety, and public accountability. The EBAA Medical Standards and Procedures are enclosed for your review. Understandably, therefore, we favor a strong commitment to medical standards and certification for the eye and tissue banking communities. To accomplish this, we urge adherence to established, proven standards developed by experts in the field; we support federally mandated compliance, and would be pleased to offer the EBAA standards as a modal for broader application. Alternatively, we would approve the adoption of discretionary language in any requirements issued for the tissue community, in order to acknowledge existing standards that work well and benefit the public.

The Medical Standards of the EBAA are subjected twice annually to strenuous review and revision by the Medical Standards Committee; in addition, our Standards are endorsed independently by the American Academy of Ophthalmology. This scientific oversight ensures a system of checks and balances which is unique in the tissue banking world.

2. Focus of Regulation (i.e., Who-or What-Should be Regulated):
We strongly support regulation or control of the banking services which support the tissue rather than regulation of the tissue itself. For instance, eye banking is an adjunct discipline of medical care, specifically ophthalmology. We provide a patient service under the direction of a physician. Our role is to deliver a cornea, not to produce it or to define the terms by which it should be used. Human corneas and other tissue are not manufactured or processed and should not be identified as a medical device; rather, the cornea is part of a service. In order to utilize existing categories within the jurisdiction of government agencies to "fit" corneas into the definition of a "device", the definition should be both biologically correct and assure quality of care in banking and distribution services.

A tissue bank is a service organization which provides for the acquisition, procurement, storage and distribution of tissue allograft. Regulation of these service entities which assist in providing the graft would appropriately focus on the following areas: registration; enforcement of standards; and tissue and tracking mechanisms. Moreover, this could be predicated on existing systems to effectuate rapidly, mandatory standards which govern:

* national registration
* peer review certification, and
* reporting of disease transmission as adverse reactions

Federal standards would be predicated on tissue operations in areas such as data collection and record review; serologic testing; credentialing; and proficiency measures.

3. Appropriate Level of Federal Oversight:
We commend the Congress and federal agencies for pursuing a proactive stance in response to the increasing concern about the potential of transmitting HIV and other infectious diseases through transplantation. The issue commands both attention and responsible action.

The EBAA mandated HIV testing as early as 1985 for all donor tissue destined for surgical use. Further in 1989, the EBAA pursued federal regulation of its laboratories under the Clinical Laboratories Improvement Act (CLIA). The EBAA has insisted on the strictest standards for screening and serological testing even though the cornea appears to be a poor vehicle for transmission of AIDS. Similarly, we have followed suit in testing for Hepatitis B and Hepatitis C to ensure patient safety, despite only a small likelihood of transmission through corneal transplantation.

Regulation, however, is not just an issue of transmission, it is also an issue of accountability and documentation. We do recognize the necessity of some form of documented accountability and recommend that such a program be introduced in an orderly, incremental fashion. We would respectfully urge the federal government to conduct a study of the existing voluntary standards prior to considering further regulation. The government may wish to examine modification of existing standards and adapting those that are appropriate, in order to assure:

* the safety and quality of tissue
* the cost effectiveness of the system, and
* the application of individual performance standards

4. Tracking and Distribution Systems within Tissue Procurement:
Over the years, the eye banking system has established an effective distribution operation, which has resulted in an average waiting time for a cornea of approximately 50 days, and which distributes eye tissue in a safe and efficacious manner. Corneal surgery is most often elective; the patient does not die for want of a transplant. In addition, current EBAA requirements for registration of donors and recipients allows for accurate tracking of this distribution. Consequently, during the recent AIDS donor crisis, we were able to respond in an immediate and complete fashion to identify the recipients of corneal tissue.

5. Training Standards for Personnel:
EBAA Medical Standards require specific training of all key personnel within the eye bank. Delegation of responsibility for the clinical work involved resides in the Medical Director; he or she must be an ophthalmologist (M.D.) who has completed a corneal fellowship or alternatively has demonstrated expertise in the relevant area. The

Medical Director must meet continuing education requirements specified by the EBAA. Each eye bank must retain at least one EBAA certified technician in a supervisory role.

EBAA Medical Standards require eye bank members to provide orientation and continuing educational opportunities. The EBAA offers a certification program for technicians twice each year. Practical and written examinations are also conducted twice each year. Certification must be renewed at least every three years and is met by attaining and documenting a specific minimum number of continuing education units (CEU's), upon approval of the EBAA Technician Committee.

6. Uniform Reporting of Suspected or Actual Incident of Disease Transmission:
A reporting structure exists through State Health Departments and the Centers for Disease Control (CDC). Use of these avenues should be encouraged and strengthened.

7. Donor Screening Criteria:
The EBAA recognizes certain inviolate universal standards for all tissue and supports testing to be performed where appropriate to remove from potential transplant the risk of disease transmission which has been proven to be transmitted through tissue transplant. Although tissues possess general similarities, the baseline, these requirements must reflect differing tissue properties; for example, uveitis for eyes; psoriasis for skin; rheumatoid arthritis for bone. There are, therefore, certain uniform criteria to which all transplant entities should adhere, but there is also a degree of flexibility and difference inherent to each tissue which must be recognized and accommodated. In these broader, less defined areas, it is the Medical Directors' expertise in the practice of medicine which must be relied upon.

We recommend granting discretion on the part of the Medical Director in order to allow latitude for specific instances of concern based on his/her knowledge of applications related to the tissue in question and its anticipated use.

We look forward to working with you in a spirit of cooperation and collaboration. Our message is simple: we urge adherence to medical standards and procedures; we recommend their implementation in a timely, and orderly fashion and would urge the government to first conduct a study of existing standards; and finally, we support regulation of the banking services which support the tissue, rather than regulation of the tissue itself.

The EBAA respectfully offers its Medical Standards as a model for broader application, or alternatively, calls for the adoption of discretionary language in any proposed legislation to acknowledge existing standards. Our Medical Standards and Procedures are enclosed for review and consideration.

Again, we thank you for the opportunity to present our views and would be pleased to contribute to the establishment of a fair and appropriate system for tissue and eye banking services in the United States.

Sincerely,

Ellen Heck

Ellen Heck, M.T., M.A.
Chairman, EBAA
Transplant Services & Eye Bank Dir.
UT Transplant Services Center &
Lions Sight & Tissue Foundation

Patricia Aiken O'Neill

Patricia Aiken O'Neill, Esq.
President/CEO, EBAA

Attachments

October 2, 1992

Senator Paul Simon
U.S. Senate
Room 462
Senate Dirksen
Office Building
Washington, DC 20510

Dear Senator Simon:

Enclosed are the official comments of the North American Transplant Coordinators Organization (NATCO) regarding S. 2906. On behalf of the organization, I wish to thank you for the opportunity to submit written testimony in response to your bill.

Sincerely,

Lisa R. Kory/lak

Lisa R. Kory, BSN, BN, CPTC
President
North American Transplant
Coordinators Organization

LRK/lak

Enclosure

RESPONSE TO S.2906

The North American Transplant Coordinators Organization (NATCO), is a professional society whose purpose is to enhance the performance of practitioners in the field of transplantation. Transplant coordinators practice in two primary areas, organ

procurement and care of the recipient patient after transplantation. NATCO's membership, exceeding 1,400, is composed of practitioners from over 300 transplant centers and 68 organ procurement organizations in the United States and others in Canada. Some of the organ procurement centers also operate tissue banks or have direct relations with other tissue banks to promote the procurement and distribution of tissue at the time of organ donation. NATCO's proactive involvement in federal and state government has enabled us to work with professional staff and elected officials to advance the field of transplantation.

NATCO participated in the FDA/DHHS public hearing on human organ and tissue transplantation held last October. NATCO continues to retain two positions on the United Network for Organ Sharing (UNOS) Board, representing transplant coordination.

NATCO is pleased to have the opportunity to submit our comments on proposed Senate Bill #2908 on human tissue regulation and the need for mandatory tissue banking standards.

Public confidence is an integral part of the organ and tissue donation process. Without public support, the donation of these vital human resources would be virtually impossible. In most cases, transplant coordinators are the direct link with the public in regard to organ and tissue donation. Therefore we actively support those policies that serve to demonstrate to the general public the safety and effectiveness of organ and tissue donation and transplantation. We are also acutely aware that recent incidents have raised some concerns regarding the safety and potential risks associated with transplantation. For these reasons, the legislation put forth by Senator Simon, S. 2908, is an important part of the process to increase organ and tissue donation in the United States. If we can continue to demonstrate to the general public that our system is based on standards and protocol that will protect the public health and not jeopardize it, the increased incidence of AIDS and other communicable diseases will not negatively effect donation efforts.

NATCO has worked collaboratively with UNOS, the American Association of Tissue Banks (AATB), and the Eye Bank Association of America (EBAA) to assure the quality of organs and tissues for transplantation. These groups have been involved with the DHHS and the CDC in preparing guidelines for the prevention of HIV transmission through transplantation of tissues and organs. This collective relationship will serve to present unified recommendations to the general public and send a clearer message of what can be done to reduce risk.

The legislation being discussed today is another attempt to provide a clear concise message on what can and should be done in regard to procurement, processing and tracking of transplanted tissues. We agree that the current position by the FDA to classify human tissue as a device is inappropriate and will result in increased cost to the health care system as well as potentially affect availability. Clinical trials, required for devices and drugs are time consuming and expensive. They serve no real purpose in the field of tissue transplantation. If the objective is to protect the public and assure safety and effectiveness, this can be accomplished by a system of standards developed by the professional community and approved by DHHS or FDA.

Although voluntary standards exist in the field of tissue transplantation, which offer a similar degree to effectiveness in identifying communicable disease, the lack of mandatory uniform testing procedures and compliance by all tissue procurement entities serve to impose problems. In addition there is wide variation in the procedures used to procure and process tissues. This variation is often not understood by members of the health care team or the

general public. There must be standardization in the processing, procurement and distribution of similar tissues to assure patient safety.

Since tissue transplantation is considered a life enhancing procedure and tissues can be preserved for longer periods of time, the standards will differ somewhat from standards for human organ transplantation which is considered life saving. Serologic testing is generally far more extensive for tissues than human organs due to the prolonged storage time afforded to tissues that is not available when maintaining human organs for transplantation. However, the implementation of standards for donor screening and tracking of recipients post transplantation should be the same for either human organs or tissues.

The recommendation to establish a National Council on Tissue Transplantation, similar to the OPTN, to develop voluntary professional standards applicable to human tissue is supported by NATCO. However, the financial resources to develop and operate such a council should come from both public and private sources (i.e. fees included in charges to private insurers for maintenance of the registry) and not divert monies needed for the delivery of health care. Membership in the council should be mandatory for all entities involved in tissue banking and eligibility criteria should not be more stringent than Medicare provider standards.

The standards and policies developed by this council should be subject to public comment before implementation and should include such issues as procurement standards (similar to standards for organ donation), processing of tissues, personnel requirements, and a tracking or monitoring system which identifies the donor and subsequent recipient and assures equitable access to all patients awaiting a tissue transplantation graft. Tissues are routinely distributed to a health care provider, not an individual recipient. In most cases the health care provider will maintain an inventory of various tissues for future use. As such, it would be difficult to track the final disposition of the tissue without assistance from the numerous health care providers involved in the process. Ultimately, the best results would be achieved with a centralized system that tracks the distribution of all tissue inclusive of not only providers but individual recipients. Although we recognize the complexity of such a system, such information is invaluable if we are to inform patients of potentially infected organs or tissues. A centralized system for documenting recipient and donor status would facilitate the timely notification of other transplant recipients when needed.

The enactment of the National Organ Transplant Act and the subsequent establishment of the Organ Procurement and Transplant Network (OPTN) have had a significant impact on the safety of organ transplantation in the United States. The existence of mandatory standards and the development of a national computer system to maintain and report data help assure the quality and safety of organs for transplantation. This system provides a solid structure for improvements as we gain more experience in this very technically complicated field. We are sensitive however to any additional regulations that could hinder progress rather than promote quality. Therefore, the creation of any new system for tissue transplantation should be simple and not impose a burden on the tissue banking industry. Complex regulations would only serve to be costly and delay positive recipient outcomes.

Successful organ and tissue donation provides optimal benefit to a patient who might otherwise die or be disabled for life. For this specialized field to remain successful the public must be assured that all policies pertaining to organ and tissue transplantation promote public safety. Federal regulations that are developed with the cooperation of the professional community, who have demonstrated their dedication and expertise in addressing many of these issues without government involvement, is essential.

If NATCO can provide additional information or clarification on any of these comments please contact Lisa Kory, President at (415) 474-0919 or Carmella Boccino, NATCO's legislative contact at (202) 347-2187.

American Academy of Orthopaedic Surgeons
317 Massachusetts Avenue, N.E. - 1st Floor • Washington, D.C. 20002
Phone: 202/546-4430 • Fax: 202/546-5051

October 2, 1992

The Honorable Paul Simon
United States Senate
Room SD-462, Dirksen Office Building
Washington, DC 20510

Dear Senator Simon:

The American Academy of Orthopaedic Surgeons (AAOS), through its nearly 15,000 members, represents the majority of physicians who transplant bone and other musculoskeletal tissues (including cartilage, ligament and tendon) and who are responsible for the medical well-being of these allograft recipients. Furthermore, many of the scientific innovations and advances associated with tissue banking and transplantation have been developed by AAOS members over the past 40 to 50 years. Therefore, the Academy has a strong interest in S.2908 and other proposals to regulate the manner in which human tissues are recovered, processed, distributed and utilized. It is of the utmost importance that these grafts be safe, efficacious and, because of their short supply, available to those most in need and in a timely, cost-effective manner.

The American Academy of Orthopaedic Surgeons feels the tissue banks:

1. must follow scientifically and clinically appropriate standards;

2. must be accredited through a program which includes on-site inspection based upon these standards and which are implemented by an independent knowledgeable group; and

3. must track tissues from donor to recipient.

While we believe the intent of S.2908 addresses these concerns, the mechanisms described by the proposed legislation are unlikely to satisfactorily accomplish these purposes.

Other issues need to be raised and explored.

- The application of musculoskeletal allografts have been rapidly expanding in response to patient care needs, notably in the treatment of tumors, joint reconstruction and sports-related trauma. Rigorous, traditional clinical

investigation and intense professional peer-group scrutiny have facilitated the safe evolution of these innovative approaches. Continued progress must be encouraged if we are to serve our patients well.

- Tissues are altruistically donated by the public with the expectation that these scarce resources will be respectfully and properly handled, equitably distributed, and not be the basis for excessive financial gain. This trust must be respected.

- If a regulatory program is established at the Federal level, particularly by the Food and Drug Administration, we may find that approaches previously designed for "biologics" or "devices" are inappropriate. Provisions that recognize the unique nature of transplantable human tissues will need to be developed.

The Academy would like to explore, with you and your staff, approaches to the banking and transplantation of human tissues in more detail. AAOS fellows have had a unique opportunity to play leadership roles in the scientific aspects of tissue transplantation, and the development of banking standards insuring safety and efficacy which are now widely used throughout the world. We have worked closely with the American Association of Tissue Banks and the American Council on Transplantation in the development of voluntary approaches to the important issues identified. Consequently, we believe there is much to be gained by a dialogue between us. Our goals remain the same as yours, the public welfare.

We are eager and prepared to meet with you in Washington, D.C. or Illinois and will contact your staff for this purpose in the future. The Academy appreciates your interest and concern.

Sincerely,

Robert N. Hensinger, M.D.

Statement of Theodore Malinin, M.D.
Prepared for the Labor and Human Resources Committee, United States Senate

Mr. Chairman and Members of the Committee, I am Theodore Malinin, M.D., Professor of Orthopaedics and Rehabilitation, and the Director of the Tissue Bank, University of Miami School of Medicine, Miami, Florida. The comments I am presenting are made on behalf of the South-Eastern Organ Procurement Foundation, Richmond, Virginia.

The South-Eastern Organ Procurement Foundation (SEOPF) is an organization with membership limited to institutions engaged in organ and tissue procurement and transplantation. Currently the Foundation is comprised of 62 institutional members. The views I would like to present are based on 23 years of cumulative experience by an organization devoted exclusively to transplantation.

Several member institutions of SEOPF have been engaged in banking of bone, skin, dura mater and other tissues since 1970. Because of concern for the safety of the patients and the efficacy of transplanted tissues, SEOPF was one of the first organizations to adopt guidelines and standards for tissue banking. Since its inception, SEOPF promulgated standards, guidelines, organizational procedures, and other regulatory procedures for organ and tissue transplantation. While the standards appear to be voluntary--they are not. Membership on

SEOPF's Bone and Tissue Committee is contingent upon rigorous inspection and verification that the tissue bank standards created by SEOPF in 1985 have been met. These standards include state-of-the-art testing for such transmissible diseases as HIV, hepatitis and other viruses, syphilis, and other bacteria and fungi. They include culture monitoring of tissue specimens at procurement, processing, and distribution. In addition, the standards make provision for first person history-taking in an attempt to identify illnesses and behavior which might preclude donation. The SEOPF standards require an autopsy on all donors, a criterion which is most stringent. Many of these standards have been adopted by other organizations within the field of tissue transplantation. SEOPF, through its tissue bank members, has fostered the introduction of standardization in the field. There are other similar endeavors from other organizations with varying levels of stringency. However, due to the absence of a uniform system within the tissue banking community and in spite of the good faith efforts of the community to promote quality, an absence of nationwide, uniform, mandatory standardization has been documented. SEOPF concurs with the findings of the PHS workshop that presently there are neither uniform guidelines nor nation-wide coordination that encompasses the field of tissue transplantation as a whole.

SEOPF went on record in advocating implementation of a unified approach which would address the entire issue of tissue donation and transplantation. SEOPF recommended a federal legislative effort which would create a mechanism through which the entire complex issue of tissue banking could be studied, and which would allow for the implementation of recommendations made by competent technical bodies such as Task Forces, Committees, Advisory Boards, etc.

SEOPF is of the opinion that concerns regarding tissue banking can be best addressed in a manner analogous to that adopted for organ transplantation.

Because of the above considerations, and because we believe several provisions of S-2906 "The Human Tissue Transplantation Act of 1992" will not benefit the patients, the South-Eastern Organ Procurement Foundation opposes the proposed legislation. The South-Eastern Organ Procurement Foundation commends Senator Simon's intention to enact legislation that would make human tissue effective and safe for human recipients. However, it does not appear that the presently proposed "Human Tissue Transplantation Act of 1992" would accomplish this purpose.

Any legislation dealing with transplantation of human tissues should recognize that uniform standards can be developed by a governmental agency in close consultation with medical practitioners and scientists, as well as with professional and technical organizations which represent transplantation endeavors. Technical matters, such as the preparation of a specific type of transplantable tissue or the matter of traceability of donors or recipients, should not be subjects of legislation. Since science and technology advance and since continuous adjustments must be made accordingly, such matters are best dealt with by a governmental regulatory agency.

Currently, the Food and Drug Administration regulates several tissues. While the regulatory rules promulgated by the FDA have created problems and difficulties with heart valve allografts, no such problems have been encountered with dura mater allografts.

SEOPF strongly opposes the concept of voluntary standards which would be enforced by federal law, and the possibility of creating another administrative structure within the Department of Health and Human Services or the creation of a National Tissue Bank Council or a similar body which would serve to inspect tissue banks for the purpose of federal licensure. To be fair, unbiased and effective licensure should be given by a disinterested governmental agency. The Food and Drug Administration has vast experience in the licensure process. Solid organ

transplantation has a well functioning, federally mandated network, which combines the very best of voluntary expertise in all areas of transplantation with the regulatory oversight of the federal government in creating a safe and effective system for all recipients. It is doubtful if regulation under another format can surpass this effort in any important way. Creation of a similar mechanism for transplantation and banking of tissues has been previously suggested by SEOPF.

In summary, SEOPF recognizes the government's responsibility to its citizens in promoting quality, safety, and efficacy in organ and tissue transplantation. As a universally recognized therapeutic modality currently available to the general public, tissue transplantation should be accessible, cost-effective, and safe for all potential recipients. By establishing federal recognition of tissue banking and transplantation and its role in the area of anatomical donation and transplantation, the individual's or family's right to decide about the full range of anatomical donation will be afforded greater national awareness and respect. In SEOPF's opinion, the legislation proposed in the "Human Tissue Transplantation Act of 1992" would not benefit the recipients of tissue transplants. For this reason SEOPF opposes the proposed bill. As an alternative SEOPF has suggested creation of a federally mandated system which has been effective in dealing with transplantation of vascularized organs.

SOUTHWEST MISSOURI THORACIC & CARDIOVASCULAR SPECIALISTS, INC.
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1965 S. FREMONT, SUITE 1200
SPRINGFIELD, MISSOURI 65804

September 30, 1992

The Honorable Paul Simon
U.S. Senate
462 Dirksen Building
Washington, D.C. 20510

Dear Senator Simon:

I was fortunate enough to be watching C-Span on the evening of 9/29/92. A program appeared in which implantable devices, particularly human allograft tissue for valve replacement, was discussed by your committee and an expert panel.

I am a practicing cardiac surgeon in Springfield, Missouri in an eight hundred plus bed hospital which has a history of performing allograft human heart valve implantations, as well as all other types of valve surgery. I would like to encourage you to follow the recommendations of the distinguished panel of physicians from the approved tissue banks and the practicing surgeons whom you interviewed.

A long history of human allograft valve implantation is present from as early as the 1960's. The Australian, as well as British, literature preceded the American experience to a great extent because of the ease with which tissue could be utilized, procured and the lack of strict regulations, allowing the surgeons in those areas to have a long and successful experience with these valves. The literature, as well as our experience, has shown that these valves are vital armamentarium in a select number of people and obviously could be utilized much more if a greater volume of tissue were available.

I would endorse the ten points made by one physician on your panel and point to the fact that, under current restrictions, it is now impossible for us to use allograft human tissue in emergency situations such as torn or dissecting aortas. We cannot meet the requirements of the FDA. The valve and valve conduit are particularly useful in people with dissecting ascending aortic arch aneurysms with valve involvement, where utilization of prosthetic material and prosthetic valves produce extensive problems of control of bleeding after implantation. These allograft valve and valve conduits offer a much greater advantage in situations such as this, greatly reducing the morbidity and mortality of death due to uncontrolled bleeding or extensive blood transfusions, as well as blood component transfusions. However, due to the restraint of a Class III device, it is impossible to get the appropriate forms and consents carried out in an emergency situation.

I would once again endorse the statements of your panel and wish that you would swiftly consider placing the human allograft valve and valve conduits on a Class II level. Thank you for your consideration in this matter. Your committee could be of great help to the medical profession in this area, as well as, providing a more expedient and safe treatment to the valve patients who would benefit by this human tissue.

Sincerely,

Fritz M. Johnson, M.D.

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

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September 25, 1992.

The Honorable Paul Simon
United States Senate
Washington D.C. 20510

FAX: (202)224-0868

Re: Senate Bill #2908

Dear Senator Simon,

Notwithstanding your well intentioned objectives I urge you to withdraw your Bill which would regulate Tissue Banks and establish a National Council on Tissue Transplantation.

This recommendation arises from a conviction that bureaucratic oversight would be an unnecessary encumbrance to an important service and would add significantly to its cost.

My interest in this issue arises from the perspective of one who pioneered the development of heart surgery in the 50's and 60's and who was one of the first to implant a prosthetic valve. I am certain that the entire field of cardiac surgery would not exist today if our progress during that period had been curtailed by the need for bureaucratic approval of each new undertaking. Hardly a week went by without an occasion that required introducing or concocting some innovation to address an unexpected problem "in the field". Indeed several of the most important and dramatic advances in heart surgery evolved either by serendipity or from the courage to try a measure that was—at the time—flagrant heresy (such as bubble oxygen-

ation, hypothermia, hemodilution, cardioplegia, foreign body implants, transplantation and circulatory arrest). F.D.A. approval for any of these modalities would have either been denied or would have taken years and huge investments to accomplish. Subsequent bureaucratic intervention has caused this exciting era of explosive development to be replaced by stagnation, trepidation and loss of U.S. leadership to Europe and Japan. Obstacles introduced by the F.D.A. to the process of applying innovative modalities are so expensive and time consuming that many are diverted from the market and patients are deprived of their benefits.

Certainly we recognize that the valuable role played by the F.D.A. in controlling the distribution of potentially toxic or dangerous drugs and devices. But expansion of that role beyond the bounds of realistic hazard becomes a disservice to humanity by curtailing the availability of measures that have a potential value that far exceeds and thoroughly justifies any potential risks. It is important to emphasize that the judgements involved in these medical innovations are not being made by innocent consumers but instead by trained and experienced specialists. These professional decision makers are not only better qualified (than any agency) to evaluate the risk/benefit ratio but also they have the strong incentive of an intimate personal involvement in the consequences. At stake is both their professional reputation and their financial resources (from malpractice litigation).

It is also important to recognize the effective protection that our profession uniquely provides to the public by universally submitting its methods and results to the critical scrutiny of peers. This mechanism was highly effective and remarkably rapid in causing unsafe or unsatisfactory modalities to be abandoned during the developmental period of cardiac surgery. It continues to operate effectively through a massive network of verbal and printed communication at multiple scientific meetings and in numerous publications.

With specific reference to the issue of tissue banks it should be pointed out that there already exists an effective mechanism for organizing, standardizing, and intercommunicating in the field. The American Association of Tissue Banks provides the functions outlined in your Bill and does so without more cumbersome paperwork and taxpayer expense.

These opinions and recommendations reflect not only my personal thoughts but also the viewpoints of the cardiovascular leadership of the entire country, with whom I have discussed the issue. I hope you will consider them to represent the best interests of our patients.

In order to acquaint you with the credentials on which these opinions are based I am attaching a condensed version of my C-V.

Sincerely Yours,

Barnas B. Ree, M.D.
Professor & Chief Emeritus

CURRICULUM VITAE OF BENSON B. ROE, M.D. (condensed)

Education:

University of California, Berkeley:	A.B.	1939
Harvard Medical School:	M.D.(cum laude)	1943
Massachusetts General Hospital:	Surgical Residency	1943-50
Dept Physiology, Harvard Med School:	National Research Fellow	1948-49
Univ Edinburgh -	Moseley Travelling Fellow (Harvard)	1950-51

Certification: Amer Board Surgery 1950; Amer Board Thoracic Surgery 1953

Title: Prof.of Surgery, University of California (Emeritus 7/89)(Active)

Professional Affiliations: 20 National and International Societies, including: Amer Surgical Assn, Amer Assn for Thoracic Surgery, Society of Thoracic Surgeons, Society of University Surgeons

Current Non-Academic Positions:
Director: Miranda Lux Foundation (President)
International Bioethics Institute.
Avery Fuller Foundation
Point Reyes Bird Observatory
Editorial Board of PHAROS
Medical Consultant for Laser Surgery Software, Inc.

Former Appointments and Positions:
Chief, Cardiothoracic Surgery, UnivCalif S.F. 1958-76 (CoChief,1976-86)
Cardiovascular Research Institute, U.C.S.F.-Senior Scientist- 1958-86
Chairman, American Board of Thoracic Surgery 1981-83 (Director 1971-83)
President, Soc of Thoracic Surgeons 1973; Chm Standards & Ethics Comm.,
President, Thoracic Surgery Directors Association 1979-81
President, California Academy of Medicine
Vice President, Society for Vascular Surgery
President, San Francisco Heart Association
Chairman, Advisory Comm for Thoracic Surg, Amer College Surgeons (3yrs)
Chairman, Thoracic Surgery Program Comm, Amer College of Surgeons (2yrs)
Coordinating Comm for Continuing Educ. in Thoracic Surgery (6yrs)
Educ Comm, Council on Cardiovasc Surg, Amer Heart Association (4yrs)
Residency Review Committee for Thoracic Surgery (6yrs)
Editorial Board, Annals of Thoracic Surgery (9yrs)
Professional Relations Committee (Fee Review), San Francisco Med Soc
Chairman, Bay Area Research Comm, Amer Heart Association (2yrs)
Board of Directors, & Exec Comm, United Bay Area Crusade (5yrs)
Liaison Committee of Amer Association for Thoracic Surgery (6yrs)
Cardiovascular Committee, Amer College of Surgeons (6yrs)
Consultant Joint Harvard-A.M.A. Resource Based Relative Value Fee Study
Councillor-at-Large, Harvard Medical Alumni Council (3yrs)
Director, Control Laser Corporation
Director, Planned Parenthood - Alameda-SanFrancisco

Visiting Professorships:
6 Medical Schools and 3 Clinics in USA and 4 other countries.
Lectures in 22 additional countries.

Bibliography: 164 publications, including: 2 Textbooks, 21 Textbook Chapters
4/91

SENATOR PAUL SIMON
SENATE LABOR AND HUMAN RESOURCES COMMITTEE HEARING
ON S2908 HUMAN TISSUE TRANSPLANTATION ACT OF 1992

September 29, 1992

As a private citizen interested in the transplantation of human tissue, I submit for your consideration a simple proposal for tracking such tissue which I would like to have included as part of the official record of the hearings.

The tracking of human tissue from donor to final recipient can be readily achieved by the incorporation of the appropriate tax identification number of each participant throughout the process.

These numbers would be added sequentially to the label on each tissue sample as it is distributed to the next participating unit as outlined below and to the medical/dental record of the recipient. All of these identification numbers are already in existance.

When an incident of disease transmission potentially attributable to the implantation of human tissue occurs, the first responsibility of the attending physician is to report to the appropriate State Department of Health. This report would include the medical/dental record of the patient from which,

using the identification numbers listed below, the complete history of the specific tissue could be reconstructed and traced back to the original retrieving unit and to the donor. This information would be immediately accessible through the identification numbers of all participating units listed in the patients' medical/record.

From the donor identification number, a properly designed computer program would reveal the location all tissue from that donor, whether in inventory, distributed to another unit or implanted in an identifiable recipient. Each unit in the process using the same computer program would be able to track from retreival to distribution and to implantation if that had occurred. The appropriate recall, quarantine or medical alert could then be issued, if necessary.

Confidentiality could be assured through encryption of all identifying numbers.

Mary St. John Douglas
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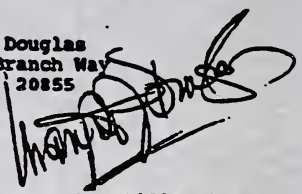

Participant	Identification
1. Donor	SSN
2. Retrieving Unit Tissue Bank(s) OPO Eye Bank Hospital	Employer I.D.
3. Processing Unit Tissue Bank(s) Processing organization Eye Bank Hospital	Employer I.D.
4. Distribution Unit Tissue Bank(s) OPO Eyebank Hospital	Employer I.D.
5. Receiving Unit (Hospital/Clinic) Hospital Clinic Physician Dentist ICU Burn Unit Research Facility	Employer I.D.
6. Implanting Unit Physician Surgeon Dentist Dental Surgeon Ophthalmologist	SSN/license number
7. Recipient Medical/Dental Record	SSN, patient number and all information above

STATEMENT OF SENATOR PAUL SIMON
INTRODUCTION OF THE HUMAN TISSUE ACT OF 1992
June 29, 1992

Mr. President, in the past several months two events have occurred that have demonstrated the need for the establishment of standards for tissue banks and for the human tissue being used for transplantation.

Recently, attention has been focused on the need for standards in the recovery and distribution of tissue as a result of the transmission of HIV from a tissue donor in Virginia to three recipients of that donor's tissue. In addition, in June 1991, the Food and Drug Administration (FDA) announced its intention to classify replacement human heart valves as medical devices and require the filing of an Investigational Device Exemption (IDE) and of a Premarket Approval Application (PMA) for this human product. For reasons set forth in a letter I directed today to FDA Commissioner David Kessler, which I will submit for the Record, this is regulatory overkill that threatens the ability of nonprofit tissue banks to continue to process human tissue.

Mr. President, these events demonstrate that the tissue banking and transplantation community should be guided by new legislation that provides an effective, workable and relatively quick standard setting process for human tissue intended for transplantation. The current authority of the Food and Drug Administration is both inadequate and inappropriate to protect the public health against concerns over safety and effectiveness of human tissue intended for transplantation. There is no uniform scheme designed to assure that donor tissue is properly tested; nor is there a mechanism to trace transplanted tissue. There is no oversight of tissue banks themselves. No national standards for processing of human tissue exist. Perhaps most important, recent regulatory efforts taken by the FDA regarding human tissue involve the imposition of premarket approval activities costing nonprofit tissue banks hundreds of thousands of dollars to demonstrate, through clinical reports, that a "product" that man did not design is safe and effective.

I have spent the last several months working with those who understand the existing regulatory mechanism for human tissue and who could guide us in developing legislation to ensure rational and effective regulation of tissue banks and human tissue itself. In so doing, my staff has analyzed the report of the Public Health Service Workgroup on organ and tissue transplantation; we have consulted informally with several organizations with expertise in tissue procurement, banking and transplantation; and we have relied on the expertise of the National Tissue Bank Council (NTBC), an organization of 18 of the largest and oldest tissue banks in the country that process the majority of human tissue intended for transplantation. More recently, our efforts have been guided by the United Network for Organ Sharing (UNOS), the organization selected by the Department of Health and Human Services (HHS) to develop criteria for the allocation of human organs in the United States. Both the NTBC and UNOS support this legislation. An explanation of UNOS' functions and its position on standards for human tissue accompanies this statement.

Mr. President, existing regulation of human tissue by FDA reflects a crazy quilted scheme, predicated upon few, if any, guiding principles. The FDA currently regulates certain cell therapies under investigational new drug applications (INDs) and intends to require the approval of a product license application for these cell therapies as biological products under the Public Health Service Act. However, unprocessed bone marrow is excluded from the FDA requirements -- although bone marrow registries and centers may shortly be subject to National Institutes of Health (NIH) regulation. Similarly, the FDA requires establishments that ship blood products interstate to be licensed as a producer of biologic products. Further, blood establishments must register and list all products they produce, and comply with regulations setting forth good manufacturing practice requirements for blood products.

In contrast, dura mater, corneal lenticules, umbilical veins, allograft cultured skin and, now, allograft human heart valves are, or are proposed to be, regulated by FDA as medical devices. The type of regulation varies considerably according to the type of tissue regulated. Some tissues, classified as medical devices, are subject only to general controls, such as good manufacturing practice requirements, including requirements related to infectious disease transmission and periodic establishment inspection. Others, such as corneal lenticules and human heart valves are required to undergo premarket approval. The PMA for corneal lenticules was submitted to FDA several years ago but has not yet been approved. The National Heart, Lung, and Blood Institute of NIH is currently preparing regulations setting forth criteria, standards, and procedures for bone marrow donor registries, bone marrow donor centers, marrow collection centers, and marrow transplant centers. In addition, the Public Health Service and the Centers for Disease Control have published periodic recommendations and guidelines relating to the transmission of communicable disease through transplantation.

Mr. President, the proposed legislation I have developed is based upon three general principles.

First, both the tissue bank community and the federal government have the responsibility to the public to assure the safety of human tissue. Thus, my bill immediately sets in motion a collaborative relationship between the tissue bank community and HHS to establish and ensure compliance with standards for tissue banks and for human tissue itself.

Second, human tissue should not be regulated as if it is an artificial product designed by man. There is no medical or scientific evidence that demonstrates a need that implantable human tissue be shown to be safe and effetive through the traditional way of regulating drugs and medical devices on a product-by-product basis. The FDA was, in effect, backed into this position in the process of regulating artificial heart valves -- perhaps without sufficient thought as to the medical and social consequences of such a decision. As I indicate in my letter to Commissioner Kessler, treating human tissue as a "product" under the medical device law is not only unnecessary to ensure safety and effectiveness, it has significant negative results for the potential availability of tissue to patients. It has severely taxed the ability of the six existing nonprofit

heart valve processors to continue to process human cardiovascular tissue, and makes it unlikely that additional nonprofit banks will be able to meet the expensive and time-consuming requirements involved in preparing IDE's and PMA's for human tissue that they process. In addition, placing human tissues under investigational status threatens reimbursement under public and private programs for the costs associated with the tissue itself, as well as for the surgical procedures involved in transplantation. I am pleased that at the urging of Commissioner Kessler, the Health Care Financing Administration (HCFA) has agreed to continue coverage of heart valve transplantation procedures under Medicare. However, if private insurance companies do not pay for human tissue under experimental status or for transplantation procedures to implant it, the availability of tissue transplantation may be severely restricted.

Third, regulation of human tissue should be by a single regulatory mechanism developed by Congress. There is no reason, in my view, why some human tissue should undergo clinical trials under a mechanism designed for drugs and sophisticated medical devices -- and under which tissue banks receive a private license to process it -- while other transplanted tissue is subject to standards applicable to all processors, and much of tissue is not subject to any standards at all. In my view, the entire field of tissue procurement, processing, and distribution should fall under a standardized approach that does not involve regulation of one tissue product at a time, but rather establishes standards for types of human tissue for clinical use. Under the current approach, it would take decades for the FDA to give scrutiny to all of the many tissues that are processed by tissue banks. There is no real utility to this approach.

A principal theme that grew out of discussions with UNOS is the desirability of significant contribution by the tissue transplant community in the development of voluntary professional standards for tissue banks and for human tissue itself. This is partially because of the fact that, at present, the majority of experience with human tissue lies outside of government. With oversight by HHS, professionals in the tissue transplant community can identify problems, establish priorities, and develop standards quickly and efficiently. In addition, there is need to ensure that federal funds not be diverted to the regulation of human tissue from other important public health efforts currently under way at the FDA.

Mr. President, let me briefly describe my proposal for new legislation. Before doing so, I want to emphasize that under the proposal, more tissue becomes subject to safety and effectiveness oversight more quickly than under the current FDA premarket approval approach. Unquestionably, therefore, the public health will be protected to a far greater extent under my proposed legislation than under the piecemeal approach with which the FDA is forced to live.

The thrust of my legislation may be summarized as follows:

First, the legislation proposes establishment of a National Council on Tissue Transplantation -- the Council -- with many responsibilities similar to that of the Organ Procurement

Transplant Network (OPTN) established under the 1984 National Organ Transplant Act, now carried out by UNOS under government contract. The primary responsibility of the Council will be to develop voluntary professional standards aplicable to human tissue banks and to human tissue itself. All tissue banks -- nonprofit and for-profit -- are eligible to join the Council; a condition of membership is to be in compliance with the Council's standards.

Second, tissue banks may become subject to requirements promulgated by the Department of Health and Human Services concerning requirements for good processing standards; requirements assuring the safe distribution of human tissue; procurement standards; maintenance of a serialized inventory system; requirements for a licensed medical director; and other requirements. Compliance with these requirements would be assured through licensure of tissue banks that process or distribute human tissue. Prior to development of mandatory regulation, however, the Secretary is to take into account whether the Council's standards provide the public with reasonable assurance of safety and effectiveness.

The third piece of the proposed legislation would address the current requirements by FDA to subject some human tissue to premarket approval requirements under the medical device law. In lieu of applying this regulatory scheme to human tissue -- which, I might add, was never in my mind when, as a member of the other body, I voted for the Medical Device Amendments of 1976 -- the bill proposes a public standard system applicable to types of classes of human tissue. Thus, rather than reviewing individual products for safety and effectiveness, public standards for types of classes of tissue must be developed by the Council, and may be required by HHS. Standards would thus replace the current system of IDEs and PMAs. It is for this reason that I am confident that under my bill, more tissue will be subject to apprpriate scrutiny in less time than under the current piecemeal approach.

In sum, Mr. President, I propose legislation that I believe better assures the public of the safety of human tissue and treats human tissue as, in effect, owned by the public -- not by individual tissue banks -- by subjecting it to voluntary and public standards applicable and available to all processors.

I ask unanimous consent that my letter to Commissioner Kessler, a statement prepared by UNOS describing its important role in organ transplantation, as well as a section analysis of the Human Tissue Transplantation Act of 1992, be inserted into the Record at this point.

102D CONGRESS
2D SESSION

S. 2908

To amend the Public Health Service Act to provide reasonable assurances that human tissue intended for transplantation is safe and effective, and for other purposes.

IN THE SENATE OF THE UNITED STATES

JUNE 29 (legislative day, JUNE 16), 1992

Mr. SIMON introduced the following bill; which was read twice and referred to the Committee on Labor and Human Resources

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A BILL

To amend the Public Health Service Act to provide reasonable assurances that human tissue intended for transplantation is safe and effective, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE, REFERENCE.

(a) SHORT TITLE.—This Act may be cited as the "Human Tissue Transplantation Act of 1992".

(b) REFERENCE.—Except as provided in section 6, whenever in this Act an amendment or repeal is expressed in terms of an amendment to, or repeal of, a section or other provision, the reference shall be considered to be

made to a section or other provision of the Public Health Service Act (42 U.S.C. 201 et seq.).

SEC. 2. REGULATION OF TISSUE BANKS AND HUMAN TISSUE FOR TRANSPLANTATION.

Part F of title III of the Act (42 U.S.C. 252 et seq.) is amended by adding at the end thereof the following new subpart:

"Subpart 3—Human Tissue

"SEC. 354. GENERAL RULES APPLICABLE TO HUMAN TISSUE.

"(a) REQUIREMENTS FOR PROCUREMENT PROCESSING OR DISTRIBUTION.—Except as provided in subsection (b), no human tissue intended for transplantation may be procured, processed, or distributed unless—

"(1) if the Secretary promulgates regulations under section 356, it is processed and distributed by one or more tissue banks in accordance with the provisions of a license; and

"(2) if it is human tissue that is subject to a public standard in effect under section 358, it meets the requirements of such standard.

"(b) APPLICATION.—

"(1) TRANSPLANTATION INTO SAME PATIENT.—The requirements of this subpart do not

apply to human tissue that is intended for transplantation in the patient from whom it is procured.

"(2) EXPEDITED TRANSPLANTATION.—The requirements of this subpart (other than section 356(a)(2)(B)) do not apply to human tissue that is not frozen after procurement and that is intended to be transplanted within 72 hours of procurement.

"SEC. 355. NATIONAL COUNCIL ON TISSUE TRANSPLANTATION.

"(a) CONTRACT.—The Secretary shall enter into a contract with a nonprofit entity that is not engaged in any significant activity unrelated to human tissue banking to establish and operate a National Council on Tissue Transplantation (hereafter referred to in this subpart as the 'Council'). The Council shall meet the requirements of subsection (c) and demonstrate the expertise necessary to carry out the functions described under subsection (f)(1)(A).

"(b) DURATION AND FUNDING.—

"(1) DURATION.—The contract required under subsection (a) shall have a duration of not less than 3, nor more than 5, years and shall be renewable.

"(2) FUNDING.—Funds for such contract shall be made available on an annual basis from funds available to the Public Health Service from appro-

priations for fiscal years beginning after fiscal year 1992.

"(c) ORGANIZATION.—The Council shall—

"(1) be a membership organization that—

"(A) consists of tissue banks and other nonprofit and for-profit entities, and persons, who procure, process, distribute or transplant human tissue; and

"(B) has as a condition of membership a requirement that, where applicable, members must meet voluntary professional standards established under subsection (f)(3); and

"(2) have a governing body that consists of not less than 12 members of which a majority must be representatives of tissue banks, and that must include representation from organ procurement organizations, voluntary health organizations, and the general public.

"(d) PERSONNEL.—

"(1) IN GENERAL.—At the request of the Council, the head of any Federal agency may detail, on a reimbursable basis, any of the personnel of such agency to the Council to assist the Council in carrying out its duties under this subpart.

"(2) SUPPORT SERVICES.—At the request of the Council, the Secretary shall provide the Council with such administrative and support services as the Council may require to carry out its duties.

"(e) EXPERTS AND PROCEEDINGS.—

"(1) EXPERTS.—In carrying out its functions, the Council may convene conferences of experts and conduct hearings.

"(2) PROCEEDINGS.—The proceedings of each meeting of the Council shall be transcribed.

"(f) DUTIES.—

"(1) REPORTS.—

"(A) INITIAL REPORT.—Not later than 6 months after the date on which the contract required under subsection (a) becomes effective, the Council shall assess the state of human tissue procurement, transportation, processing, storage and distribution, and prepare and submit to the Secretary a report that includes—

"(i) an assessment of public and private efforts to procure human tissue for transplantation and an identification of the sources of such tissue;

"(ii) a description of the extent and types of tissue banks in the United States;

"(iii) an assessment of problems in coordinating the procurement of viable human organs and human tissue; and

"(iv) recommendations for the education and training of health professionals, including physicians, nurses, and hospital and emergency care personnel, with respect to human tissue procurement.

"(B) ANNUAL REPORT.—The Council shall prepare and submit to the Secretary an annual report containing information on the extent of its activities and the results of its efforts during the year for which the report is being submitted.

"(2) ROUTINE DUTIES.—The Council shall—

"(A) collect and make available the latest scientific information on donor screening, processing methodology, and other issues relating to the safety of human tissue intended for transplantation;

"(B) identify all human tissue processors and tissue distributors and provide them an opportunity to become members of the Council;

"(C) collect, analyze, and publish data concerning human tissue donation and transplants;

"(D) carry out studies and demonstration projects for the purpose of improving procedures for human tissue procurement and processing and identifying usable types of human tissues;

"(E) work actively to increase the availability of types of donated human tissue that are determined to be in short supply;

"(F) assess the need for the establishment of a system for the distribution of human tissue in short supply in the United States and, if the Council determines that a system should be established, develop criteria for such a system; and

"(G) develop a uniform method of recordkeeping that permits the identification of each recipient of transplanted human tissue in the United States, facilitates the retrieval of potentially infectious tissue, and protects the confidentiality of recipient and donors of such tissue.

"(3) DEVELOPMENT AND DISSEMINATION OF PROFESSIONAL STANDARDS.—The Council shall—

"(A) not later than 6 months after the date on which the contract required under sub-

section (a) becomes effective, develop voluntary professional standards that meet the requirements of section 356(a)(2)(B), relating to the procurement of human tissue from donors in order to provide reasonable assurances that such tissue does not transmit disease;

"(B) not later than 18 months after the date on which the contract required under subsection (a) becomes effective, develop voluntary professional standards that meet the requirements of section 356(a)(2)(E) governing the processing and distribution of human tissue by tissue banks;

"(C) at the request of the Secretary, or on its own initiative, periodically develop and submit to the Secretary voluntary professional standards for a type or types of human tissue together with a comprehensive report providing the basis for such standards;

"(D) not later than 6 months after the date on which the contract required under subsection (a) becomes effective, submit a proposed public standard for human heart valves that meets the requirements of section 358; and

"(E) widely disseminate the voluntary professional standards developed under subparagraphs (A), (B), (C), and (D).

"(g) PROCEDURES FOR RECEIPT AND CONSIDERATION OF COMMENTS.—The Secretary shall establish procedures for—

"(1) receiving from interested persons comments relating to the manner in which the Council is carrying out the duties required under this title; and

"(2) the consideration by the Secretary of such comments.

"SEC. 355A. REGISTRATION.

"(a) PROMULGATION OF REGULATIONS.—

"(1) IN GENERAL.—The Secretary may by regulation require that on or before December 31 of each year, every tissue bank, and every entity (other than a tissue bank) that procures human tissue within a State shall register with the Secretary and provide the information required under subsection (b).

"(2) CONTENT.—Regulations promulgated under paragraph (1) shall require that every tissue bank (or other entity described in paragraph (1)) prior to engaging in the procurement, processing or

distribution of human tissue in a State shall register with the Secretary and provide the information required under subsection (b).

"(b) REQUIRED INFORMATION.—Information required to be provided under subsection (a) shall include—

"(1) the name and location of the tissue bank or other entity;

"(2) if the tissue bank or other entity is a partnership, the name of each partner;

"(3) if the tissue bank or other entity is a corporation, the name of each corporate officer and director, and the state of incorporation;

"(4) the type or types of human tissue procured, processed or distributed by the tissue bank or other entity; and

"(5) such other information as the Secretary determines is necessary for the protection of the public health.

"SEC. 356. LICENSURE.

"(a) PROMULGATION OF REGULATIONS.—

"(1) IN GENERAL.—The Secretary may, taking into consideration voluntary professional standards developed by the Council under section 355(f)(3) (A) and (B), and after providing notice and opportunity for comment, promulgate regulations prohibiting a

tissue bank from processing or distributing human tissue that is intended for transplantation unless the tissue bank holds a valid license issued under subsection (c) and operates in accordance with the license. Such regulations may impose varying requirements for different services performed with respect to human tissue processed or distributed by such banks.

"(2) CONTENT.—Regulations promulgated under paragraph (1) shall include—

"(A) provisions for the issuance of licenses to tissue banks that provide that if an accreditation body is designated under section 356A, such tissue banks shall have the option of applying for a license directly from the Secretary or seeking accreditation by such body;

"(B) a requirement that any human tissue procured by the tissue bank be procured in accordance with regulations prescribed by the Secretary that are designed to provide reasonable assurance that such tissue does not transmit disease;

"(C) a requirement that any tissue bank that receives human tissue from an entity other than a tissue bank licensed under this section

have a written agreement with such entity that tissue received by the tissue bank is procured in accordance with requirements established under subparagraph (B);

"(D) requirements for the maintenance of appropriate records, including pertinent medical records and test results;

"(E) requirements that human tissue be processed and distributed in accordance with good tissue banking procedures that are designed to provide reasonable assurances that human tissue processed or distributed by the tissue bank does not transmit disease;

"(F) a requirement for the establishment of a serialized inventory system that is consistent with the uniform method of recordkeeping established under section 355(f)(2)(G), that permits the identification by donor of all human tissue procured, processed or distributed by the tissue bank and maintains records concerning the disposition of all such human tissue;

"(G) provisions setting forth qualifications for tissue bank personnel, including a requirement that each tissue bank have a medical di-

rector or medical officer who is a physician licensed to practice medicine in a State; and

"(H) a requirement that a tissue bank be incorporated in a State or territory or the District of Columbia and have a board of directors (or be part of an entity that is so incorporated and has a board of directors).

"(b) EFFECTIVE DATE OF REQUIREMENT.—The requirements of subsection (a) with respect to licensure shall not become effective until 1 year after the promulgation of final regulations under this section.

"(c) PROCESS.—

"(1) APPLICATION.—A license for a tissue bank shall be issued under this subsection if—

"(A) an application therefor has been submitted to the Secretary which contains or is accompanied by such information as the Secretary reasonably determines is necessary; and

"(B) the Secretary determines that—

"(i) the tissue bank meets the requirements of regulations promulgated under this section; or

"(ii) the tissue bank is accredited in accordance with section 356A.

"(2) PERIOD OF LICENSE.—A license issued under this subsection shall be valid for an initial period of 3 years and shall be renewable for periods of 3 years thereafter upon a showing that the tissue bank continues to meet licensure requirements under this section.

"(3) DECLARATIONS OF LICENSE.—

"(A) A license issued under this subsection shall specify whether the tissue bank is authorized to engage in the processing or distribution of human tissue (or both such activities).

"(B) A license issued under this subsection shall specify the types of human tissue that may be processed or distributed by the tissue bank for which the license is in effect.

"(4) REQUIREMENT OF SEPARATE LICENSES.—Regulations promulgated under this section shall require a separate license for each physical facility that processes human tissue.

"(5) FEES.—

"(A)(i) The Secretary shall require the payment of fees by a tissue bank for the issuance and renewal of licenses and for inspections of such tissue banks.

"(ii) Fees imposed under clause (i) shall be sufficient to cover the costs of the Secretary in implementing the Secretary's responsibilities under this section and section 357.

"(B) An accrediting body may require the payment of fees by a tissue bank to cover the costs of performing accreditation activities under section 356A.

"(C) Fees imposed under subparagraphs (A) and (B) shall vary by type of tissue bank, based on considerations such as dollar volume and type or class of human tissue processed or distributed by such tissue banks.

"SEC. 356A. ACCREDITATION.

"(a) IN GENERAL.—A tissue bank may be accredited for purposes of obtaining a license under this subpart if the tissue bank—

"(1) meets the standards of the accreditation body designated under subsection (b); and

"(2) authorizes the accreditation body to submit to the Secretary such records or other information as the Secretary may require.

"(b) ACCREDITATION BODY.—

"(1) REQUIREMENTS.—The Secretary may designate one or more nonprofit organizations to serve

as the accreditation body for the accreditation of tissue banks if—

"(A) using inspectors qualified to evaluate the methods used by such tissue banks for the procurement, processing and distribution of human tissue, the accreditation body agrees to inspect a tissue bank for purposes of accreditation with such frequency as determined appropriate by the Secretary;

"(B) the standards applied by the body in determining whether or not to accredit a tissue bank are equal to or more stringent than the standards issued by the Secretary under section 356;

"(C) there is adequate provision for assuring that the standards of the accreditation body continue to be met by the tissue bank;

"(D) in the case of any tissue bank accredited by the body that has had its accreditation denied, suspended, withdrawn, or revoked or that has had any other action taken against it by the accrediting body, the accrediting body agrees to submit to the Secretary the name of such tissue bank within 10 days of the action taken;

"(E) the accreditation body agrees to notify the Secretary at least 30 days prior to changing its standards; and

"(F) after having its designation withdrawn by the Secretary, the body agrees to notify each tissue bank accredited by the body of the withdrawal within 10 days of the withdrawal.

"(2) ENTITY AS COUNCIL.—An accrediting body under this section may be the entity that contracts with the Secretary to establish the National Council on Tissue Transplantation under section 355.

"(3) PROCEDURES.—The Secretary shall promulgate criteria and procedures for the designation of accreditation bodies and for the withdrawal of such designations, if the Secretary determines that the accreditation body does not meet the requirements of paragraph (1).

"(4) WITHDRAWAL OF DESIGNATION.—If the Secretary withdraws the designation of the accreditation body under paragraph (1), the license of any tissue bank accredited by the body shall continue in effect for 60 days after the tissue bank receives notification of the withdrawal of the designation, except

that the Secretary may extend such period for a tissue bank if the Secretary determines that the tissue bank submitted an application for a license in a timely manner after the receipt of the withdrawal of designation.

"(5) WITHDRAWAL OR REVOCATION OF LICENSE.—

"(A) If an accreditation body withdraws or revokes the license of a tissue bank, the Secretary shall, within 45 days after the tissue bank receives notice of such action, determine whether the tissue bank meets the requirements promulgated under section 356 and, based on such determination, issue or deny a license to the tissue bank.

"(B) The license of a tissue bank that has been revoked or withdrawn shall remain in effect until such license is issued or denied under subparagraph (A).

"(6) ANNUAL EVALUATION.—The Secretary shall periodically evaluate the performance of an accreditation body designated under subsection (b) by—

"(A) inspecting, under section 357, a sufficient number of the tissue banks accredited by

such body to allow a reasonable estimate of the performance of such body; and

"(B) such other means as the Secretary deems appropriate.

"(7) INSPECTION.—Inspection of tissue banks by an accrediting body shall be in accordance with section 357.

"SEC. 357. INSPECTIONS.

"(a) PROCEDURE.—

"(1) AUTHORITY.—The Secretary may, at reasonable times and in a reasonable manner, enter and inspect tissue banks subject to the licensure requirements set forth in section 356 for the purpose of—

"(A) licensing such facilities under section 356;

"(B) determining the performance of an accrediting body designated under section 356A(b); or

"(C) inspecting a facility accredited under section 356A, on a determination that such inspection is necessary for the protection of public health.

"(2) ACCESS.—

"(A) Except as provided in subparagraph (B), in conducting inspections under this sec-

tion, the Secretary shall have access to all facilities, equipment, materials, records, and information having a bearing on whether the tissue bank meets the requirements of section 356, or whether human tissue subject to the requirements of a public standard established under section 358 meets such standard.

"(B) No inspection authorized by this section shall extend to financial data, service fee data, or research data.

"(b) IDENTIFICATION.—An inspection under this section may be made only upon presenting proper identification to the owner, operator, or agent in charge of the tissue bank being inspected.

"SEC. 358. STANDARDS FOR HUMAN TISSUE.

"(a) VOLUNTARY PROFESSIONAL STANDARDS.—

"(1) IN GENERAL.—The Secretary shall, following the receipt of a voluntary professional standard for a type or types of human tissue from the Council under section 355(f)(3)(C), publish in the Federal Register such voluntary standard and provide interested persons the opportunity to submit comments thereon.

"(2) REQUIRED COMMENTS.—In carrying out paragraph (1), the Secretary shall request comments

on whether compliance with a voluntary professional standard submitted by the Council is sufficient to provide patients with reasonable assurances of the safety and effectiveness of the type or types of human tissue that is the subject of such voluntary professional standard.

"(b) PUBLIC STANDARD.—

"(1) REGULATIONS.—If the Secretary determines that the use of a voluntary professional standard for human tissues that is submitted by the Council under section 355(f)(3)(C), is insufficient to provide patients with reasonable assurances of the safety and effectiveness of the type or types of human tissue that is the subject of the voluntary professional standard, the Secretary shall promulgate a regulation establishing a public standard for such tissue.

"(2) REQUIREMENTS.—

"(A) Public standards established under regulations promulgated under paragraph (1) shall be designed to provide reasonable assurances of the safe and effective performance of the type or types of human tissue covered by the public standard.

"(B) Public standards may be based on evidence from controlled investigations, partially controlled studies, well documented case histories, reports of clinical experience in humans, or other evidence which qualified experts may conclude constitutes adequate scientific evidence to support such standards.

"(3) SUPPORTIVE DATA.—The data required under paragraph (2) to support public standards may vary according to—

"(A) the characteristics of the type of human tissue covered by the standard;

"(B) the indications for use of the human tissue;

"(C) the information to be provided to physicians or other health care professionals in the labeling of such tissue; and

"(D) the extent of experience with the use of such tissue for transplantation in humans.

"(4) CONTENTS OF STANDARDS.—Public standards established under this section shall contain provisions that—

"(A) apply to the processing of the specific type or types of human tissue covered by the public standard and that, where feasible and

consistent with the public health, authorize alternative methods of processing;

"(B) where appropriate, specify physical and biological properties of such tissue; and

"(C) specify labeling requirements.

"(5) EFFECTIVE DATE.—A regulation establishing a public standard under this section shall contain the date or dates on which the public standard shall take effect, but shall not set forth a date prior to 1 year after the promulgation of the regulation unless the Secretary determines that an earlier effective date is necessary for the protection of the public health.

"(6) AMENDMENTS.—After consultation with the Council, the Secretary may, after providing notice and opportunity for comment and on an expedited basis where appropriate, amend a public standard to reflect new technology, or for other reasons determined appropriate.

"SEC. 359. ENFORCEMENT.

"(a) IN GENERAL.—

"(1) FAILURE TO REGISTER.—Any tissue bank or other entity that is required to register under section 355A and that fails, within a reasonable time after written notification by the Secretary, to correct

any registration violation, shall be subject to a civil penalty of not more than $10,000 per violation.

"(2) FAILURE TO LICENSE.—Any tissue bank that violates regulations established under section 356 and that fails, within a reasonable time after written notification by the Secretary, to correct any such violation shall be subject to a civil penalty of not more than $25,000.

"(3) FAILURE TO COMPLY WITH PROCUREMENT STANDARDS.—Any entity that procures human tissue in violation of regulations prescribed by the Secretary under section 356(a)(2) and that fails, within a reasonable time after written notification by the Secretary, to correct such violation shall be subject to a civil penalty of not more than $25,000.

"(4) FAILURE TO COMPLY WITH PUBLIC STANDARDS.—Any person who introduces or delivers for introduction into interstate commerce human tissue that is subject to a public standard in effect under section 358 that does not meet such standard shall be subject to a civil penalty of not more than $50,000.

"(b) ASSESSMENT OF PENALTIES.—

"(1) ORDER AND HEARING.—A civil penalty imposed under paragraph (2), (3), or (4) of subsection

(a) shall be assessed by the Secretary by an order made after providing an opportunity for an informal hearing. Prior to issuing such an order, the Secretary shall give written notice to the tissue bank, or person to be assessed the civil penalty under such order, of the Secretary's intention to issue such order and provide the tissue bank or person an opportunity to request, within 15 days of the date the notice is received by the tissue bank, such a hearing on the order.

"(2) REMITTANCE OR MITIGATION.—Any civil penalty imposed under this section may on application be remitted or mitigated by the Secretary.

"(3) CONSIDERATION OF GRAVITY OF VIOLATION.—In determining the amount of a civil penalty under this section or whether it should be remitted or mitigated and in what amount, the Secretary may consider the gravity of the violation.

"(c) SUSPENSION OF LICENSE.—

"(1) AUTHORITY.—A license issued under section 356(c) for a tissue bank may be suspended on the order of the Secretary if the Secretary determines, after providing an opportunity for an informal hearing to the owner or operator of the tissue

bank, that such tissue bank (because of the actions of its owner or operator or any employee or agent)—

"(A) has been guilty of misrepresentation or an intentional omission of a material fact in obtaining the license;

"(B) has failed to comply with requirements under subsections (a) and (b) of section 356; or

"(C) has failed to comply with the reasonable requests of the Secretary for any information relevant to making a determination whether the tissue bank has committed a violation described in subparagraph (A) or (B);

and that such person has failed, within a reasonable time after written notification by the Secretary, to bring the tissue bank into compliance with the regulations or the terms of the license.

"(2) CONTINUATION OF SUSPENSION.—Any suspension of a license pursuant to paragraph (1) shall continue in effect until the conditions giving rise to the suspension have been corrected as evidenced by a written submission to the Secretary and the completion of a satisfactory inspection of the tissue bank that was subject to the suspension. The Secretary shall promptly review any written submis-

sion made pursuant to this paragraph and, if the submission is determined to be satisfactory, shall conduct an inspection and issue an order continuing or lifting the suspension.

"(3) ADDITIONAL SANCTIONS.—In lieu of the sanctions prescribed under this subsection, the Secretary may (after the opportunity for informal hearing and notification), impose one or both of the following sanctions on a tissue bank for a violation of such subsection:

"(A) A directed plan of correction.

"(B) Payment for the costs of on site monitoring by representatives of the Secretary.

"(d) SEIZURE OF HUMAN TISSUE.—Human tissue that is subject to a public standard in effect under section 358 and that does not meet such standard, shall be seized in accordance with the provisions of section 304 of the Federal Food, Drug, and Cosmetic Act.

"SEC. 360. JUDICIAL REVIEW.

"Judicial review of regulations promulgated under sections 356 and 358, orders granting or refusing licenses under subsection 356(c), any final action taken by the Secretary under section 359(a), orders issued by the Secretary pursuant to sections 359(b) and 359(c), seizure action taken under 359(d), and orders under section

351(d)(2)(A) relating to human tissue, shall be in accordance with section 517 of the Federal Food, Drug, and Cosmetic Act.

"SEC. 360A. EFFECT ON STATE LAWS.

"(a) IN GENERAL.—Except as provided in subsection (b), nothing in this subpart shall be construed as affecting the power of any State or political subdivision of a State to enact and enforce laws relating to tissue banks regulated under this subpart to the extent that such laws are not inconsistent with the provisions of this subpart or regulations promulgated thereunder.

"(b) EXCEPTION.—No State or political subdivision of a State may establish or continue in effect with respect to human tissue intended for transplantation any requirement—

"(1) which relates to the safety and effectiveness of a type or types of human tissue required under a public standard under section 358; and

"(2) which is different from, or in addition to, any requirement under such public standard.

"(c) ACTION AS A SERVICE.—This subpart shall not be construed as in any way affecting State law treating the procuring, processing, storage, distribution, or transplantation of human tissue as a service.".

SEC. 3. RECORDS OF TRANSPLANTATION.

Title III is amended by inserting after section 399A (42 U.S.C. 280c–5) the following new part:

"PART M—HUMAN TISSUE

"SEC. 399B. RECORDS OF TRANSPLANTATION.

"The Secretary may, after receiving the recommendations of the Council established under section 355, for a uniform method of recordkeeping under subsection (f)(2) of such section, prescribe regulations requiring that providers of services or other entities that participate in programs established under title XVIII or XIX of the Social Security Act, as a requirement of their participation in such programs, establish and maintain records relating to the transplantation of human tissue in their facilities, including the maintenance of records of transplantation of such tissue in a manner that—

"(1) facilitates the identification of patients who have received the transplanted human tissue, donors of such tissue and the distributor of such tissue; and

"(2) includes the labeling of such tissue.".

SEC. 4. DEFINITIONS.

Section 2 (42 U.S.C. 201) is amended by inserting after subsection (q) the following new subsections:

"(r) The term 'human tissue' means human material intended to be transplanted in another human which con-

sists of bone, ligaments, tendons, cartilage, nerves, skin, veins, arteries, dura mater, connective tissue and heart valves, and other human material designated by the Secretary by regulation. Such term includes human material described in the preceding sentence in combination with substances used for the purpose of maintaining cell viability, including cryoprotectants, tissue culture media, organ preservation solutions, and other material having no pharmacological effect. Such term does not include—

"(1) vascularized vital organs such as hearts, livers, kidneys, lungs, intestines, or pancreas;

"(2) blood, corneas, bone marrow, semen, or analogous materials;

"(3) human genes or genetic material; or

"(4) human material used solely for diagnostic or research purposes.

"(s) The term 'tissue bank' means a person who processes or distributes human tissue intended for transplantation.

"(t) The term 'distribute' means the transferring of human tissue after processing to the facility at which such tissue is transplanted.

"(u) The term 'informal hearing' means a hearing described in section 201(y) of the Federal Food, Drug, and Cosmetic Act.".

SEC. 5. CONFORMING AMENDMENTS.

(a) REGULATION OF BIOLOGICAL PRODUCTS.—Section 351(d)(2)(A) (42 U.S.C. 262) is amended by inserting after "section" the following: ", or human tissue (as defined in section 2(r)),".

(b) PART HEADING.—The part heading for part F of title III is amended to read as follows:

"PART F—REGULATION OF BIOLOGICAL PRODUCTS, CLINICAL LABORATORIES AND HUMAN TISSUE".

SEC. 6. REGULATORY STATUS OF HUMAN TISSUE.

(a) REGULATION UNDER EXISTING AUTHORITIES OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT.—

(1) Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)(1)) is amended by adding at the end thereof the following new sentence: "Such term does not include human tissue as defined in section 2(r) of the Public Health Service Act.".

(2) Section 201(h) of such Act (21 U.S.C. 321(h)) is amended by inserting the following after "purposes" the second time it appears: ", but does not mean human tissue as defined in Section 2(r) of the Public Health Service Act.".

(b) REGULATION AS A CLINICAL LABORATORY.—A tissue bank that is licensed under section 356 of the Public Health Service Act is, with respect to its activities re-

garding human tissue, not subject to regulations promulgated under section 358 of such Act.

SEC. 7. TRANSITIONAL PROVISIONS FOR HUMAN HEART VALVES.

(a) ENFORCEMENT REGULATIONS.—The Secretary of Health and Human Services may not enforce the regulation of the Food and Drug Administration promulgated on May 13, 1987 (52 Federal Register 18162) insofar as such regulation is applicable to human heart valves.

(b) RESCISSION OF REGULATION.—The determination by the Food and Drug Administration that human heart valves are replacement heart valves subject to a requirement for premarket approval published on June 26, 1991 (56 Federal Register 29177) is hereby rescinded.

SEC. 8. EXPEDITED PUBLIC STANDARD FOR HUMAN HEART VALVES.

(a) INITIATION OF PROCEEDING.—Not later than 60 days after the development of a voluntary standard under section 355(f)(3)(D) of the Public Health Service Act, the Secretary of Health and Human Services shall initiate a proceeding under section 358 of such Act to determine whether a public standard applicable to human heart valves should be established.

(b) EXPEDITED PROCEEDING.—The proceeding referred to under subsection (a) shall be expedited.

O

STATEMENT OF THE
UNITED NETWORK FOR ORGAN SHARING
CONCERNING
THE HUMAN TISSUE ACT OF 1992

Organ donation and tissue donation depend on public support and confidence. In many cases, organs and tissues are donated at the same time. Donated organs were designated as a public resource by the National Organ Transplant Act of 1984. Donated tissues must be treated as a public resource in order to protect the integrity of organ and tissue donation and transplantation in the Unted States.

Transplantable human organs are in short supply. Patients are dying at an accelerating rate while waiting for an organ transplant. National efforts to educate the public and medical professionals on the merits of organ donation are underway. Since organ and tissue donation are so closely linked, both functionally and in the eyes of the public, care must be taken to coordinate organ donation with tissue donation.

The National Organ Procurement and Transplantation Network (OPTN), with all United States organ transplant centers and organ procurement organizations (OPOs) as members, establishes voluntary policies for organ procurement, organ allocation and other essential aspects of organ transplantation. The OPTN has been in operation since September 30, 1986, and is operated by the United Network for Organ Sharing (UNOS), a not-for-profit corporation, under contract with the Department of Health and Human Services. UNOS operates a self-regulating professional organization that depends primarily on the volunteer efforts of members, with support from a full-time staff. UNOS is also the contractor for the organ transplantation scientific registry.

Organ procurement organizations designated by the Health Care Financing Administration, of which there were 68 as of June 1, 1992, handle all organ procurements and a substantial portion of all tissue procurements. All OPOs are

members of the OPTN and adhere to its organ procurement and allocation policies . As efforts are made to increase the rate of organ donation and to expand the traditional donor pool to help solve the organ shortage, organ procurement becomes more complex and demanding. Unless tissue procurement is governed in a manner similar to, and compatible with, organ procurement, there will be inevitable damage to organ procurement.

Tissue transplantation has been allowed to develop without significant federal regulatory involvement. The discovery of the human immunodeficiency virus (HIV) and its increasing incidence in the population has focused much greater attention on testing both organ donors and tissue donors for HIV. It is now time for Congress and the Department of Health and Human Services to bring tissue procurement under federal government oversight. Borrowing significantly from the experience of the OPTN, the Human Tissue Act of 1992 would bring tissue procurement, processing and distribution under the control of the Department of Health and Human Services through a contract relationship with a private not-for-profit entity for operation of the National Council on Tissue Transplantation (NCTT). The NCTT will be a membership organization that sets voluntary standards for tissue procurement, processing and distribution; collects and publishes scientific information; and collects data concerning tissue transplantation. If the experience of the NCTT parallels that of the OPTN, compliance with voluntary standards will become pervasive and effective. Voluntary standards will keep pace efficiently with scientific and technological advances and will assure safety and effectiveness without the necessity for promulgation of mandatory regulations, if the tissue transplantation community works together within the framework of the National Council on Tissue Transplantation. If volunteer standard-setting is not effective, the Act authorizes HHS to adopt regulations to require registration, licensing and inspection of tissue banks, tissue processors, and tissue distributors as needed.

The NCTT will also be able to address problems that relate to a scientific type of human tissue, such as human heart valves, by adoption of voluntary standards. If HHS finds that these voluntary standards are not effective to solve the problems, it may promulgate mandatory public standards relating to that type of tissue.

There have thus far been relatively few concerns with the safety and effectiveness of human tissue transplantation or of organ transplantation. It is hoped that the establishment of a voluntary standard-setting organization for human tissue, to work in cooperation with the existing organ network, will allow both organ and tissue transplantation to continue to operate safely and effectively under government oversight, but without the need for significant government effort or expense.

United States Senate
WASHINGTON, DC 20510-1302

June 26, 1992

David A. Kessler, M.D., Commissioner
Food and Drug Administration
5600 Fishers Lane
Parklawn Building, Room 14-17
Rockville, MD 20857

Dear Commissioner Kessler:

I wanted to let you know that on Monday, June 29, I will introduce the Human Tissue Act of 1992, which will provide direction to the Food and Drug Administration in the regulation of human tissue.

I look forward to working with you on this important legislation and believe its enactment will provide your agency more appropriate and flexible tools with which to assure the American public of the safety and effectiveness of human tissue intended for transplantation. I have asked Senator Kennedy to schedule hearings on the proposed legislation in the next few weeks.

As you know, on several occasions I have expressed my concern over the implications of FDA's decision to regulate human heart valves as class III medical devices. While I take no position on the legality of this action, it is my view that requiring clinical trials for products made from human tissue was never contemplated by Congress, and this action poses immense problems related to costs. Your efforts in securing continued Medicare coverage for heart valve replacement surgery are commendable, but these efforts do not guarantee coverage by private insurance plans, which typically exclude "investigational" products from coverage.

In addition, I am advised that the current expense of compliance with the requirement to hold investigational device exemptions (IDEs) by nonprofit tissue banks is well in excess of $10,000 per month, per tissue bank. These increased costs, I am told, have been passed on to recipients, with the result that the cost of a human heart valve today is at least 50 percent greater than the cost one year ago.

Moreover, one of the six tissue banks that processes human heart valves has, for financial reasons, dropped out of the consortium of tissue banks pursuing a common IDE. It is entirely possible that, if the requirement to conduct clinical trials is continued, several nonprofit tissue banks will abandon the field to existing for-profit processors. Clearly, the action requiring premarket approval is inconsistent with the spirit of the 1984 National Organ Transplant Act, which prohibits the commercialization of human organs and tissue.

My legislation would authorize the FDA, after consideration of voluntary professional standards developed by a National Council on Tissue Transplantation, to develop public standards for human tissue, as well as standards for licensure of tissue banks. In my view, this approach would result in the application of standards, either voluntary or prescribed by the FDA, in a relatively short period of time -- certainly much shorter than an approach involving the application of clinical trials on a tissue-by-tissue basis. Because the legislation adopts an approach to the deregulation of human tissue most consistent with that required by human blood and other biological products, it precludes regulation of any human tissue as either a medical device or a new drug.

I have serious doubts that requiring clinical trials yields any greater protection of the public health than would well-designed standards. As stated by Richard Hopkins, M.D., Director of Pediatric Cardiac Surgery, Georgetown University Medical Center, "allograft valves were made and designed by God. From an engineering standpoint, they are the most perfect we have." Your own letter to Acting HCFA Administration Toby acknowledges that "FDA has no evidence of significant safety problems involving the current use of these devices...." Statements such as these clearly call into question the need for expensive and time-consuming clinical trials.

Because of the pendency of the proposed legislation, and my commitment to its enactment, I believe it would be wholly appropriate for FDA to suspend its decision to regulate human heart valves as class III medical devices, and I urge you to take action to do so. It may be that this action could be accompanied by assurances by the tissue banks that they will continue to comply with processing protocols that are now required under the IDE.

I am eager to learn of your response to this suggestion, and await your reply.

My best wishes.

Cordially,

Paul Simon
U.S. Senator

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

JUL 2 . 1992

The Honorable Paul Simon
United States Senate
Washington, D.C. 20510

Dear Senator Simon:

This is in response to your letter of June 26, 1992, regarding the regulation of human tissue and allograft heart valves by the Food and Drug Administration (FDA). Let me assure you that we appreciate the many difficult issues related to this area, as well as your continuing interest and concern.

In 1991, the Public Health Service (PHS) established a Workgroup on Organ and Tissue Transplantation (the Workgroup) to evaluate the need for additional Federal regulation of organ and tissue transplantation practices and the risk of infectious disease transmission. There are nine Federal agencies, including FDA, participating in the Workgroup. In July 1991, the Workgroup issued an assessment report of the Federal government's responsibility for protecting the public health from infection associated with organ and tissue transplantation. The Workgroup defined the universe of organ and tissue transplantation, estimated the risks of infection with transplantation, and identified how Federal, State, and voluntary guidelines control those risks. This report, which I have attached for your information, outlines the Workgroup's findings and identifies unresolved issues.

On October 16, 1991, the PHS convened a public hearing to gain insight from the industry and the public on these issues. Several organ procurement organizations, tissue banking organizations (including the National Tissue Bank Council) and individual tissue banks, health professional groups, research oriented organizations, and patient advocacy groups participated.

Witnesses at the hearing expressed a clear desire and need for additional Federal regulation in the area of tissue banks, but there was uncertainty about how this could best be accomplished. Some participants advocated measures to reduce the risk of infectious disease transmission that would include, at a minimum, registration, donor screening, and recordkeeping. The Workgroup is completing its report and will transmit it soon to the Assistant Secretary for Health.

As you are aware, FDA has regulated certain human tissues under current statutory authority contained in the Public

Health Service Act and the Federal Food, Drug, and Cosmetic Act (FD&C Act). For example, blood, a human tissue, has been regulated as a biological product and as a drug product under these statutes for many years. Other tissue-derived products, such as human hormones, have also been regulated as drugs and as biologics. More recently, FDA has regulated three types of human tissue allografts pursuant to the general statutory provisions for regulation of medical devices in the FD&C Act. In addition to human heart valves, human dura mater (brain membrane material) and corneal lenticules (corrective lenses derived from corneal tissue) are regulated as medical devices.

FDA is now regulating heart valve allografts as class III medical devices subject to the regulation (21 CFR 870.3925) governing all replacement heart valves. On June 26, 1991, a notice was published in the Federal Register clarifying that the rule governing all replacement heart valves includes allograft replacement heart valves. A group of non-profit processors of allograft valves have petitioned the United States Court of Appeals for the Seventh Circuit for a determination of the validity of this notice.

As explained in the June 26, 1991 notice, there are a number of unresolved issues concerning disease transmission, processing, and durability of allograft valves which remain unanswered, despite the fact that various forms of allograft valves have been in use for over twenty-five years. The following brief historical background may help explain the developments that have led to FDA regulation of human heart valves.

With the development of reliable cardiopulmonary bypass techniques, cardiac surgeons began investigating various means of performing corrective surgery to repair damaged or diseased native heart valves. Many different replacement valves and repair procedures have been developed over the last 30 years. To date, there is no replacement heart valve on the market, including allograft heart valves, that provides performance and durability equivalent to a normal original heart valve.

Allograft heart valves removed from cadavers were first used in the 1960's in Great Britain and Australia because of perceived design advantages. However, some of those valves did fail, resulting in death or re-operation for patients.

Recovered valves can only rarely be transplanted directly from recently deceased donors to recipients. To solve problems related to valve selection, sizing, sterilization, storage, transportation, and delivery, a number of different preservation and processing techniques have been used, some of which were unsuccessful and had to be abandoned -- for instance, a form of "tanning," as done for leather goods, using glutaraldehyde, and the use of high concentrations of antibiotics in a cold storage solution.

Over the last 20 years, despite the existence of a number of studies of individual aspects of processing, there were no comprehensive controlled studies of any processing or storage method. A number of questions unique to the safety, durability, and functioning of allograft heart valves still remain, and FDA believes that oversight is necessary to deal with these questions.

When FDA requested data validating the usefulness and safety of various techniques, no processing center was able to file a pre-market approval application (PMA) to provide those data. FDA therefore suggested that processing centers submit their processing protocols as investigational device exemptions (IDEs) to permit the continued distribution of the valves. [illegible] that the prospective collection of data through IDEs will permit validation of particular processing techniques. These are the clinical trials to which your letter refers. In the absence of objective clinical trials, neither FDA nor processing centers can assure that safe and effective techniques are being used.

FDA has taken several steps to minimize burdens imposed on tissue banks by the decision to regulate heart valve allografts as class III medical devices. Several extensions of the effective date have been granted by which processors of heart valve allografts must have a filed PMA or IDE to continue processing and marketing these valves. In response to a petition from a group of non-profit allograft processors who have filed an IDE, FDA extended the initial effective date of August 26, 1991, first to November 25, 1991, then May 31, 1992, and finally to June 30, 1992. The stays were based on FDA's determination that there is a public health interest in maintaining patient access to heart valve allografts during the regulatory process. As of April 20, 1991, petitioners informed FDA's Center for Devices and Radiological Health that 111 of the 159 proposed sites had obtained institutional review board (IRB) approval for IDE status, and approvals were in final stages at three additional sites. In addition, Cryolife-Cardiovesculer, Inc., a for-profit processor that has also filed an IDE, stated that as of April 20, 1992, it did not need additional time to secure IRB approvals because it had obtained approvals for 5 principal investigational sites and 242 secondary sites.

On July 1, 1992, in response to a petition for a stay filed by the non-profit processors, the Seventh Circuit Court of Appeals ordered a further stay of the effective date of enforcement of the requirement that allograft valves be marketed under either an approved PMA or IDE, until such time as it rules on the validity of the June 26, 1991 notice.

FDA believes that every center performing allograft heart valve processing has had adequate time to submit an IDE which describes the processing protocol that each center believes most appropriate based on experience and the limited information in the literature.

FDA also shares your concern about public access to these medical devices as this relates to the availability of reimbursement. We have been working with the Health Care Financing Administration (HCFA) to continue coverage under Medicare for these valves while they are under an IDE. HCFA has assured us that coverage will continue under the present circumstances. While we are aware that other third party payors are not bound by HCFA's decision, its guidelines are often used as a reimbursement standard by other payors. This decision may, therefore, provide a basis for others to continue coverage.

Please be assured that we share your goal of establishing the most effective system for regulating human tissue that balances access to human tissue products with protection of the public health.

Thank you for your interest in this issue. Please contact me if we may be of further assistance.

Sincerely yours,

Marc J. Scheineson
Associate Commissioner
for Legislative Affairs

THE HIV TRANSMISSION ISSUE
Simon Staff Information Paper
September 29, 1992

BACKGROUND. Since 1985, donors of organs or tissues have been screened routinely for HIV-1. In 1991, however, seven persons who had received transplanted tissue or organs from one donor were found to be HIV positive. This case has raised policy concerns about donor screening, tissue processing, and recordkeeping.

THE CASE. In 1991, a woman whose only risk factor for HIV was the receipt of a bone allograft in December 1985 was identified as being infected. Investigation revealed the donor was a 22-year-old man who died after being shot in the head. Four organs and 54 other tissues had been distributed from the donor. The donor had tested negative for HIV and interviews with his family members had not revealed risk factors for HIV infection. Two women sex partners had tested negative for HIV. One woman sex partner declined to be interviewed or to be tested for HIV.

Of the 58 tissues and organs obtained from the donor, an accounting could be made for 52. Of the 48 identified recipients, 41 were tested for the HIV antibody. All four recipients of organs and all three recipients of unprocessed fresh-frozen bone were infected with HIV. The 34 recipients of other tissues -- involving 2 corneas, 3 treated soft tissue, 25 ethanol-treated bone, 3 radiation treated dura mater, and 1 fresh-frozen bone from which the marrow had been removed -- tested negative for HIV. Subsequent tests on cultured lymphocytes from the donor tested positive for HIV.

Of the eight pieces of tissue not traced to recipients, one piece had been destroyed by the hospital, and one piece was impounded upon discovery; hospitals that received them have been unable to account for six pieces of the tissue.

Three of the four organ recipients and two of the fresh-frozen bone recipients were known as early as 1986 to be HIV positive, but no connection was made with the donor. Factors such as multiple blood transfusions were suspected. Not until 1991, during a routine review of 1990 hospital discharges, was a 78-year-old woman recipient of bone for hip replacement identified as being infected with HIV-1, and the allograft identified as the only possible source of infection.

HEART VALVE ALLOGRAFT REGULATION

Simon Staff Information Paper, 10/92

CURRENT STATUS

FDA has recently been given the authority by the courts to continue to impose its regulation of human heart valves under the Medical Devices Act.

Six nonprofit heart valve processors filed suit in the Court of Appeals of the Seventh Circuit asking for a stay of the FDA regulations on heart valves on the grounds that the FDA had violated the Administrative Procedures Act by covering human heart valves under an existing set of regulations for mechanical devices. (Appeals courts have jurisdiction over application of the Administrative Procedures Act.) The Court granted the stay while it examined the issue.

On September 16, the Court withdrew its stay. The Court decided it had no jurisdiction to entertain the petition to review the Notice of Applicability of a Final Rule (NAFR) published by FDA. The Court found it lacked jurisdiction because the NAFR is an interpretation of an existing rule rather than a new rule, and that human heart valves can reasonably be construed to be covered by the rule. In making that determination, the Court noted that Congress had defined "device" to include an "implant" and that the term "implant" is defined in medical terminology to include living or inert human tissue.

HISTORY

On February 5, 1980, the FDA issued a final ruling regulating replacement heart valves. In this ruling, the FDA defined replacement heart valves as "valves constructed of prosthetic materials, biologic valves (e.g., porcine valves), or valves constructed of a combination of prosthetic and biologic materials." In 1987, FDA issued a final regulation requiring premarket approval of replacement heart valves by December 9, 1987. There is no evidence that when these regulations were promulgated, FDA intended that they apply to heart valves made from human tissue (allografts). (In 1987 FDA informed at least one allograft valve processor that the regulation was not intended to cover them.)

On June 26, 1991, the FDA submitted notice of a final rule requiring Premarket Approvals (PMAs) and Investigational Device Exemptions (IDEs) for heart valve allografts. The notice was of applicability of the regulations promulgated in 1987, and provided 60 days for processors to have approved IDEs or PMAs. Processors were to have their PMAs approved by August 26, 1991 in order to bypass the IDE process. In response to a petition from a group of nonprofit allograft processors, FDA extended the initial effective date first to November 25, 1991 and finally to June 30, 1992.

There have been 7 processors of human heart allografts in the U.S.: 6 nonprofit tissue banks and one for-profit company. As of April, 111 of 159 sites served by the nonprofits had obtained institutional review board approval for IDE status. Cryolife Cardiovascular, Inc., a for-profit processor, had obtained approvals for 5 principal investigational sites and 242 secondary sites. For financial reasons, one of the six tissue banks dropped out of the nonprofit consortium pursuing a common IDE.

THE GENERAL PROBLEM

By regulating allograft valves in this manner, FDA did not allow heart valve processors a 30 month grace period in which to file a PMA, the procedure specifically required by statute and provided to mechanical valve manufacturers under the 1980 regulation.

In its final ruling, the FDA deviated from the recommendations made by the Circulatory System Devices Advisory Panel by requiring prospective trials and IDEs for heart valve allografts. The Advisory Panel recommended development of PMAs with use of retrospective data and literature.

Although allograft processors agreed that heart valve allografts should be regulated, they argued that the FDA final rule would not give them sufficient time to comply with PMA requirements.

THE IDE DISADVANTAGE

Investigational Device Exemptions may severely restrict the supply of heart valve allografts on a nationwide basis. Payment for these devices usually comes from private reimbursers who do not cover surgeries involving IDE devices. Blue Cross/Blue Shield has a written policy that prohibits the financing of surgeries with IDE devices. Commissioner Kessler has written to the Health Care Financing Administration (HCFA) stating that the valves are safe and asking that Medicare coverage continue to be available for them while they are under an IDE. Other third party payors, however, are not bound by HCFA's decisions. Any reduction in heart valve allografts would increase the risks to children and pregnant women with heart problems since allografts are considered the only viable medical alternative for them.

APPROPRIATE REGULATION

Allograft processors argue the existing regulatory structure is not the most appropriate way to regulate allograft valves. The PMA process is designed to assure safety and effectiveness of devices and includes evaluation of materials, design, manufacturing processes and other elements not applicable to human tissue. The primary reasons for regulating tissue are to assure against disease transmission and to ensure good practices by tissue banks. These factors are generally applicable to all tissues, while the PMA requirements are specific to each individual device. Allograft processors urge the development of regulations addressing the specific characteristics of tissue use.

MEDICAL COMMUNITY

The medical community believes that appropriate regulation of heart valve allografts will have positive results. Dr. Richard A. Jonas, Associate Professor of Surgery at Harvard Medical School, points out, however, that "even the slightest interference with the availability of the human valve at this crucial time would result in a definite increase in operative mortality for complex conditions."

According to information provided to the Circulatory Systems Advisory Panel, there are approximately 1400 to 1500 valves presently processed, and this is an inadequate number to meet current demand -- thus any delay in making them available would have a significant impact.

Our hearing stands adjourned.
[Whereupon, at 11:19 a.m., the committee adjourned.]

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